Australian Government
Department of Health
Office of the Gene Technology Regulator

Risk Assessment and Risk Management Plan (Consultation version) for

DIR 180

Commercial supply of a genetically modified COVID-19 vaccine

Applicant: AstraZeneca Pty Ltd

18 December 2020

This RARMP is open for consultation until 18 January 2021.

Written comments on the risks to human health and safety and the environment posed by this proposed supply of the GM COVID-19 vaccine are invited. You may make your submission

via mail to: The Office of the Gene Technology Regulator, MDP 54 GPO Box 9848, Canberra ACT 2601

or

via email to: ogtr@health.gov.au.

Please note that issues regarding the patient's safety and the quality and efficacy of the vaccine do **not** fall within the scope of these evaluations as they are the responsibilities of other agencies and authorities.

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Summary of the Risk Assessment and Risk Management Plan

(Consultation Version) for

Licence Application DIR 180

Introduction

The Gene Technology Regulator (the Regulator) has received a licence application (DIR 180) for import, transport, storage and disposal of a genetically modified (GM) COVID-19 vaccine, as part of its commercial supply as a human vaccine. These activities are classified as Dealings involving the Intentional Release (DIR) of genetically modified organisms into the Australian environment under *the Gene Technology Act 2000*.

Before the GM vaccine can be used, AstraZeneca must also obtain regulatory approval from the Therapeutic Goods Administration (TGA). Therapeutic goods for sale in Australia must be included in the Australian Register of Therapeutic Goods (ARTG) under the *Therapeutic Goods Act 1989*. The TGA would assess patient safety and the quality and efficacy of the vaccine prior to including the GM vaccine on the ARTG. In addition, approval from the Department of Agriculture, Water and the Environment will also be required for import of the GM vaccine.

The Regulator has prepared a Risk Assessment and Risk Management Plan (RARMP) for this application, which concludes that the proposed supply of the GM vaccine poses negligible risks to human health and safety and the environment. Licence conditions have been drafted for the proposed supply. The Regulator invites submissions on the RARMP, including draft licence conditions, to inform the decision on whether or not to issue a licence.

The application

Application number	DIR-180
Applicant	AstraZeneca Pty Ltd
Project title	Commercial supply of a genetically modified COVID-19 vaccine[1]
Parent organism	Chimpanzee adenovirus Y25

Introduced gene and modified trait	• Deletion of:
	  ○ E1 gene (renders virus unable to multiply)
	  ○ E3 gene (increases immune response to virus and virus production during manufacture)
	• Partial substitution of E4 gene with the corresponding gene from the human adenovirus 5 (improves virus yield during manufacture)
	• Insertion of a gene encoding codon-optimised full length SARS-CoV-2 spike protein (expresses spike protein)

Previous clinical trials	Phase 1/2 clinical trial with the GM vaccine ChAdOx1-S [recombinant] (also known as AZD1222, ChAdOx1 nCoV-19) was conducted and completed in the United Kingdom (UK) to test the safety of the vaccine in adults aged 18-55 years.
Current approvals	• Clinical trials with the GM vaccine ChAdOx1-S [recombinant] (also known as

[1] The title of the licence application submitted by AstraZeneca is "Commercial release of a COVID-19 vaccine AstraZeneca to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)".

	AZD1222, ChAdOx1 nCoV-19) are approved and are currently ongoing in several overseas jurisdictions including the UK, the United States (US), Brazil, South Africa, Argentina, Chile, Colombia, Japan, Peru and the Russian Federation. • The GM vaccine may be manufactured in Australia under Dealings Not involving Intentional Release (DNIR) of a GMO into the environment (DNIR-630 and DNIR-632) or imported under a Notifiable Low Risk Dealing. • The GM vaccine is currently not approved for commercial supply in any region or country.
Proposed locations	Australia-wide
Primary purpose	Commercial supply of the GM COVID-19 vaccine

Risk assessment

The risk assessment concludes that risks to the health and safety of people or the environment from the proposed supply, either in the short or long term, are negligible. No specific risk treatment measures are required to manage these negligible risks.

The current assessment focuses on risks posed to people other than the intended vaccine recipient and to the environment, including long term persistence of the GMOs, which may arise from the import, transport, storage or disposal of the GMO. The risk assessment process considers how the genetic modification and activities conducted with the GM vaccine in the context of import, transport, storage and disposal might lead to harm to people or the environment. Risks are characterised in relation to both the seriousness and likelihood of harm, taking into account information in the application, relevant previous approvals, current scientific knowledge and advice received from a wide range of experts, agencies and authorities consulted on the preparation of the RARMP. Both the short and long term risks were considered.

Credible pathways to potential harm that were considered included: whether people and animals can be exposed to the GMO and whether there is a potential for the GMO to recombine with other similar viruses or to get genes from those viruses. The potential for GMO to be released into the environment and its effects was also considered.

The principal reasons for the conclusion of negligible risks associated with import, transport, storage and disposal of the GMO are:

- The GMO is replication incompetent which will prevent it from multiplying in other cells;
- The GMO would be restricted to the site of injection and/or draining lymph nodes and would not be shed from the vaccine recipients;
- The GMO does not cause disease in humans and other organisms other than great apes;
- The likelihood of accidental exposure to the GMO in people not being vaccinated (non-vaccinees) would be minimised due to well-established import, transport, storage and disposal procedures; and
- The likelihood of complementation and recombination of GMO with other adenoviruses is very low.

Risk management

The risk management plan concludes that risks from the proposed dealings can be managed so that people and the environment are protected by imposing general conditions to ensure that there is ongoing oversight of the vaccine containing the GMO.

Risk management is used to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan evaluates and treats identified risks and considers general risk management measures. The risk management plan is given effect through licence conditions.

As the level of risk was assessed as negligible, specific risk treatment is not required. However, the Regulator has drafted licence conditions regarding post-release review (post-market surveillance) to ensure that there is ongoing oversight of the supply of the GM COVID-19 vaccine and to allow the collection of ongoing information to verify the findings of the RARMP. The draft licence, detailed in Chapter 4 of the consultation RARMP, also contains a number of general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, which include an obligation to report any unintended effects.

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Abbreviations

AICIS	Australian Industrial Chemicals Introduction Scheme
AdV	Adenovirus
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARTG	Australian Register of Therapeutic Goods
BAC	Bacterial artificial chromosome
CAR	Coxsackie and adenovirus receptor
ChAd	Chimpanzee adenovirus
ChAdOx1	Chimpanzee adenovirus type Oxford University 1
COVID-19	Coronavirus disease 2019
DAWE	Department of Agriculture, Water and the Environment
DIR	Dealings involving Intentional Release
DNA	Deoxyribonucleic acid
EU	European Union
FSANZ	Food Standards Australia New Zealand
g	gram
GM	Genetically modified
GMO	Genetically modified organism
GTTAC	Gene Technology Technical Advisory Committee
HAdV	Human adenovirus
HGT	Horizontal gene transfer
IATA	International Air Transport Association
IM	Intramuscular
kb	Kilobase pair of DNA
ml	Milli litre
NSW	New South Wales
OGTR	Office of the Gene Technology Regulator
Orf	Open reading frame
PCR	Polymerase chain reaction
QLD	Queensland
RARMP	Risk Assessment and Risk Management Plan
RNA	Ribonucleic acid
S	Spike
SAdV	Simian adenovirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TGA	Therapeutic Goods Administration
the Act	The *Gene Technology Act 2000*
the Regulations	The Gene Technology Regulations 2001

the Regulator	The Gene Technology Regulator
tPA	Tissue plasminogen activator
UK	United Kingdom
USA	United States of America
WA	Western Australia
WHO	World Health Organization

Chapter 1 Risk assessment context

Section 1 Background

1. An application has been made under the *Gene Technology Act 2000* (the Act) for Dealings involving the Intentional Release (DIR) of genetically modified organisms (GMOs) into the Australian environment.

2. The Act and the Gene Technology Regulations 2001 (the Regulations), together with corresponding State and Territory legislation, comprise Australia's national regulatory system for gene technology. Its objective is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.

3. Section 50 of the Act requires that the Gene Technology Regulator (the Regulator) must prepare a Risk Assessment and Risk Management Plan (RARMP) in response to an application for release of GMOs into the Australian environment. Sections 50, 50A and 51 of the Act and sections 9 and 10 of the Regulations outline the matters which the Regulator must take into account and who must be consulted when preparing the RARMP.

4. The *Risk Analysis Framework* (RAF) (OGTR, 2013) explains the Regulator's approach to the preparation of RARMPs in accordance with the Act and the Regulations. The Regulator has also developed operational policies and guidelines that are relevant to DIR licences. These documents are available from the Office of the Gene Technology Regulator (OGTR) website.

5. Figure 1 shows the information that is considered, within the regulatory framework above, in establishing the risk assessment context. This information is specific for each application. Risks to the health and safety of people or the environment posed by the proposed supply are assessed within this context. Chapter 1 describes the risk assessment context for this application.

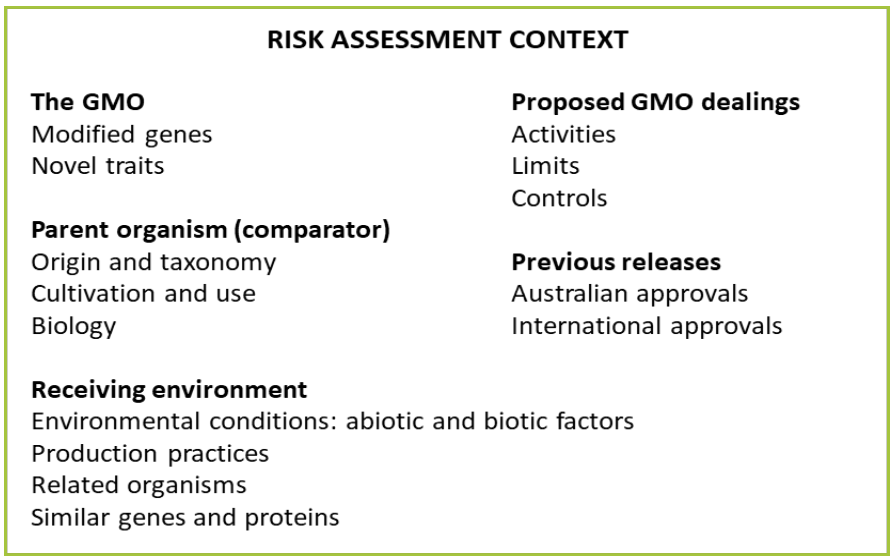

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

6. This application does not meet the criteria for a limited and controlled release application under section 50A of the Act. Therefore, under section 50(3) of the Act, the Regulator was required to seek advice from prescribed experts, agencies and authorities on matters relevant to the preparation of the RARMP. This first round of consultation included the Gene Technology Technical Advisory Committee (GTTAC), State and Territory Governments, Australian Government authorities or agencies prescribed in the Regulations and the Minister for the Environment. A summary of issues contained in submissions received is provided in Appendix A.

7. Section 52 of the Act requires the Regulator to seek comment on the RARMP from the experts, agencies and authorities outlined above, as well as the public through a second round of consultation.

1.1 Interface with other regulatory schemes

8. Gene technology legislation operates in conjunction with other regulatory schemes in Australia. The GMOs and any proposed dealings conducted under a licence issued by the Regulator may also be subject to regulation by other Australian government agencies that regulate GMOs or GM products, including Food Standards Australia New Zealand (FSANZ), the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Therapeutic Goods Administration (TGA), the Australian Industrial Chemicals Introduction Scheme (AICIS) and the Department of Agriculture, Water and the Environment (DAWE).

9. The TGA provides a national system of controls for therapeutic goods. It administers the provisions of the *Therapeutic Goods Act 1989* which specifies the standard that must be met before a vaccine can be registered on the Australian Register of Therapeutic Goods (ARTG). Inclusion in ARTG is required before a vaccine can be lawfully supplied in Australia. As part of this process, the TGA would assess the quality, safety and efficacy of the vaccine. Quality aspects could include batch-to-batch consistency in vaccine composition, purity and potency. Safety aspects could include toxicological and allergenicity profile of the vaccine, including any excipients, by-products and impurities from manufacture.

10. The administration/use of GMOs as therapeutics is not regulated under gene technology legislation. The Regulator does not assess vaccine excipients and would not assess manufacturing by-products and impurities unless they are themselves GM products.

11. The labelling, handling, sale and supply of scheduled medicines is regulated through the *Scheduling Policy Framework for Medicines and Chemicals* (AHMAC, 2018). Guidelines for the safe handling, storage and distribution of Schedule 4 medicines such as vaccines are specified through the *Australian Code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8* (NCCTG, 2011). The provisions of this Code, which ensure that quality is maintained during wholesaling, are applied through applicable State and Territory therapeutic goods/drugs and poisons legislation, and/or State or Territory wholesaler licensing arrangements.

12. To avoid duplication of regulatory oversight, risks that have been considered by other regulatory agencies would not be re-assessed by the Regulator.

13. **For the commercial supply of a GM COVID-19 vaccine, dealings regulated under the Act include the import, transport, storage and disposal of GMOs. The Regulator has assessed risks to people as a consequence of conducting these activities and risks from persistence of the GMOs in the environment.**

Section 2 The proposed dealings

14. SARS-CoV-2 is a novel coronavirus discovered in December 2019 in Wuhan, Hubei province of China and is the cause of the COVID-19 disease. As this virus quickly spread around the world, the World Health Organization (WHO) declared the outbreak a public health emergency of international concern (PHEIC) on the 30th January 2020 and eventually a pandemic on 11th March 2020 (WHO - Timeline of WHO's response to COVID-19, 2020).

15. The most common symptoms of COVID-19 are fever, tiredness and a dry cough, although some patients develop aches and pains, nasal congestion, runny nose, sore throat or diarrhoea. Symptoms are usually mild with gradual onset and about 80% of infected people recover without specific treatment. However, COVID-19 can cause complications such as severe pneumonia, acute respiratory distress syndrome, and multiple organ failure and in some cases, death. This is especially in older patients and those with pre-existing respiratory or cardiovascular conditions. There is currently no vaccine available for COVID-19 in Australia but as of 8th December 2020, 52 candidate vaccines are in clinical evaluation

around the world (WHO -Draft landscape of COVID-19 candidate vaccine, 2020). These vaccines are based on a variety of platforms such as lipid nanoparticles mRNA, DNA, adjuvant protein, inactivated virus particles and non-replicating viral vectors.

16. AstraZeneca Pty Ltd (AstraZeneca) is seeking authorisation of the commercial supply of a genetically modified (GM) COVID-19 vaccine (ChAdOx1-S [recombinant], also known as AZD1222 and ChAdOx1 nCoV19) to occur Australia-wide. No COVID-19 vaccine, GM or non-GM is currently approved for commercial supply in Australia as of 18th December 2020.

17. The proposed vaccine is to prevent coronavirus disease – 2019 (COVID-19) caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals.

18. For the ongoing commercial supply of the GM vaccine, the dealings assessed by the Regulator are:

(a) import the GMO;

(b) transport the GMO;

(c) dispose of the GMO

and the possession (including storage), supply or use of the GMO for the purposes of, or in the course of, any of the above.

2.1 Details of the proposed dealings

19. GM vaccine would be distributed to a variety of facilities which offer vaccination services in all Australian States and Territories. The GM vaccine would be administered by intramuscular injection.

20. The vaccine would be supplied as a multi-dose vial with up to 10 doses per vial (volume up to 5 ml). These vials will be packed into cartons followed by packaging into shipping boxes for distribution.

21. The GM vaccine may be manufactured overseas, in Australia or a combination of both to meet the target supply. An import permit from the DAWE would be required for the vaccine manufactured overseas.

22. The storage and handling of both imported and Australian manufactured GM vaccine would be in accordance with the *Australian Code of Good Wholesaling Practice for Medicines in schedules 2, 3, 4 and 8* (TGA, 2011) and the WHO *Good distribution practices for pharmaceutical products* (WHO, 2010). Further, the Australian manufactured GM vaccine would also be subjected to storage and transport requirements of the DNIR licence approved by the Regulator.

23. The transport within Australia (i.e., distribution to vaccination sites) for both imported and Australian manufactured GM vaccine would be conducted by a commercial courier company experienced in the transportation of pharmaceutical products such as vaccines.

24. Storage of the GM vaccine at vaccination sites and other facilities will be conducted according to the National Vaccine Storage Guidelines (Department of Health, 2019) and the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP, 2020) which includes maintenance of the ‘cold chain’ and restriction of access to pharmacy and other authorised personnel.

25. The GM vaccine would be administered as an intramuscular injection at vaccination sites. Following administration, all residual vaccine and associated waste which has come in to contact with GM vaccine (such as syringes and swabs) will be discarded into clinical and related waste. Similarly, unused expired vaccine would be disposed of at vaccination or storage facilities in accordance with the relevant State and Territory legislation procedures for clinical/medical waste disposal methods such as high temperature incineration.

Section 3 Parent organism

26. The GM vaccine contains a Chimpanzee Adenovirus type Oxford University 1 (ChAdOx1) vaccine vector which is derived from modified chimpanzee adenovirus isolate Y25 (ChAd Y25). ChAd is a member of the genus *Mastadenovirus* in the *Adenoviridae* family. Adenoviruses (AdVs) are classified as Risk Group 2 microorganisms (Standards Australia/New Zealand, 2010). The characteristics of the parent organism provide a baseline for comparing the potential for harm from dealings with the GM vaccine. As such, the relevant biological properties of ChAd Y25 will be discussed here.

27. Human adenoviruses (HAdVs) are categorised into seven species A to G based on their serology, sequence homology, serum neutralisation, hemagglutinin properties and genome sequence (Ismail et al., 2018; Lange et al., 2019; Bots and Hoeben, 2020). Simian adenoviruses (SAdVs) are isolated from great apes (chimpazees, bonobos and gorillas) and are found to be generally similar to HAdVs, therefore, SAdVs are grouped within the HAdV species B, C, E and G (Dicks et al., 2012; Lange et al., 2019).

28. HAdV species E has only one member isolated from humans i.e., HAdV-4 (Dicks et al., 2012; Gray and Erdman, 2018; Lion, 2019) but includes several ChAds which are being evaluated for use as vaccines (Dicks et al., 2012). As there is limited information available on ChAds, much of the parent organism information has been based on HAdVs as they are closely related.

3.1 Pathology

29. ChAd Y25 is classified into HAdV species E and is a principal cause of mild respiratory tract infections in the great apes (Lange et al., 2019). ChAd Y25 is also known to cause gastrointestinal tract and eye infections in great apes.

30. ChAds are not isolated from humans but neutralising antibodies to ChAds have been detected in people suggesting that humans may become infected with ChAds (Xiang et al., 2006). The detection of antibodies against ChAd and SAdVs in the general population represents prior exposure to chimpanzees or are due to cross-reactive HAdVs antibodies (Xiang et al., 2006; Hoppe et al., 2015). However, those exposed to ChAd are clinically asymptomatic (Xiang et al., 2006), therefore, ChAds are not known to cause any disease in humans.

31. HAdVs are common pathogens of humans and cause a wide range of illnesses such as the common cold, sore throat, bronchitis, pneumonia, diarrhoea, conjunctivitis, fever, inflammation of the stomach, intestine and bladder and neurologic disease (conditions that affect the brain and spinal cord) (Public Health Agency of Canada, 2014; CDC - Adenoviruses, 2019).

32. HAdV infection is generally mild and self-limiting. Overall, HAdV infections are responsible for about 2-5% of all respiratory infections in humans (Allard and Vantarakis, 2017). HAdV species E are the most common cause of human respiratory diseases and eye diseases (Ghebremedhin, 2014; Ismail et al., 2018).

33. Outbreaks of HAdVs-associated respiratory disease are more common in the late winter, spring and early summer, however infections can occur throughout the year. After natural HAdV infection, the incubation period of HAdVs ranges from 2 days to 2 weeks, depending on the viral species and serotype as well as the mechanism of acquisition (Public Health Agency of Canada, 2014; Allard and Vantarakis, 2017). For respiratory infections, the incubation period is generally 4-8 days whereas 3-10 days for intestinal infections (Allard and Vantarakis, 2017). The symptoms of mild infection usually last for a few days to a week but for the severe infections, symptoms may last longer.

3.2 Structure and genomic organisation

34. AdVs are non-enveloped, double-stranded DNA viruses with an icosahedral surface shell (capsid) and a core that contains DNA. The genome of AdVs has approximately 30-35 kilobases (kb) which includes 30-40 genes (Lasaro and Ertl, 2009; Charman et al., 2019). The genome is flanked by inverted terminal repeats (ITRs).

35. HAdVs and ChAds have a similar genome organisation (Roy et al., 2004) with the exception of some variations in the coding sequences located in the E3 gene.

36. The HAdV genome contains early and late genes which are organised into transcription units (Figure 2). Early genes/regions (E1, E2, E3 and E4) are involved in directly activating transcription of other viral regions, altering the host cellular environment to enhance viral replication, and co-ordination of viral DNA replication (Roy et al., 2004; Lasaro and Ertl, 2009; Afkhami et al., 2016; Saha and Parks, 2017). The late genes (L1 to L5) encode components of the viral shell and other proteins that are involved in assembly of the capsid and are essential for production of new virus particles.

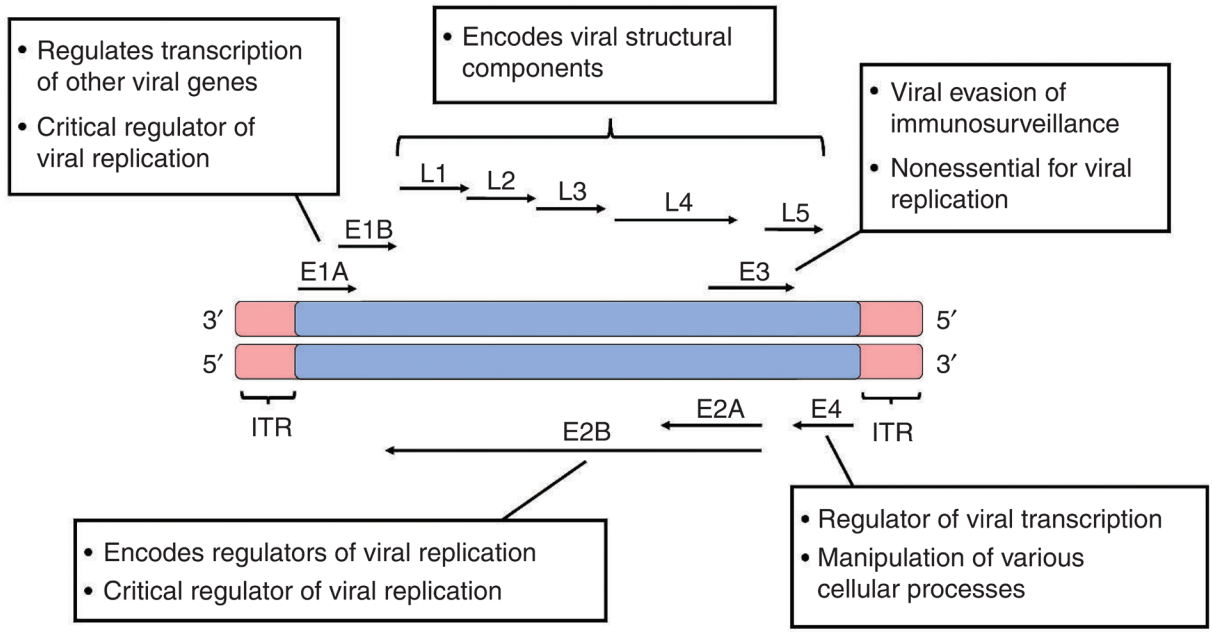

Figure 2: **Functions, organisation and structure of adenovirus genome (Afkhami et al., 2016).**

37. The E1 gene is composed of E1A and E1B. The E1A gene controls transcription of viral genes and redirects host-cell gene expression machinery to enable virus replication. The E1A gene products are the first proteins expressed from the infecting virus, and are essential for the efficient expression of other viral genes (Roy et al., 2004; Saha and Parks, 2017). The E1B gene assists in viral replication and is mainly required for the export of viral late mRNA (L1 to L5) from the host-cell nucleus into the cytoplasm. Together the E1A and E1B coding regions are essential for viral gene expression and replication (Roy et al., 2004; Saha and Parks, 2017).

38. The E2 gene is sub-divided into E2A and E2B that encode E2 proteins which are mainly involved in viral DNA replication and transcription of late genes (Roy et al., 2004; Saha and Parks, 2017). The E3 gene encodes viral proteins that destabilize host immune responses i.e., modulates immune response. The E4 gene modulates cellular function and assists with viral DNA replication and RNA processing.

3.3 Viral infection and replication

39. AdVs can infect a wide range of cells and tissues and replicate efficiently in both dividing and non-dividing cells. AdVs most frequently infect epithelia of the upper or lower respiratory tract, eyes, gastrointestinal and urinary tract tissues.

40. HAdVs uses the Coxsackie-adenovirus receptor (CAR) transmembrane proteins, CD46, CD80, CD86 and saliac acid to enter the host cells (Zhang and Bergelson, 2005; Lion, 2019). HAdV species C and E use the Coxsackie-adenovirus receptor (CAR) transmembrane proteins as the main receptor to gain entry to a variety of different cell types (Zhang and Bergelson, 2005; Lasaro and Ertl, 2009; Morris et al., 2016;

Bots and Hoeben, 2020). Similarly, ChAds also use the CAR protein for entry into the host cells (Morris et al 2016)(Morris et al., 2016; Bots and Hoeben, 2020).

41. The replication of AdVs takes place in the nucleus of the host cell and uses the host cell nuclear machinery to make copies of itself (Figure 3). Briefly, the AdV attaches to the receptors present on the cell membrane leading to internalisation of the virus by endosomal uptake. The virus is then uncoated resulting in the release of viral particles. The viral genome is transported into the nucleus where the transcription occurs (described above in para 37 and 38; (Charman et al., 2019)). The viral DNA replication occurs in the nucleus before transport into the cytoplasm where viral structural proteins are made. The new virus particles are then assembled. Finally, the host cell breaks apart releasing the viruses (Waye and Sing, 2010b). Progeny viruses released from infected cells usually do not spread further than the regional lymph nodes.

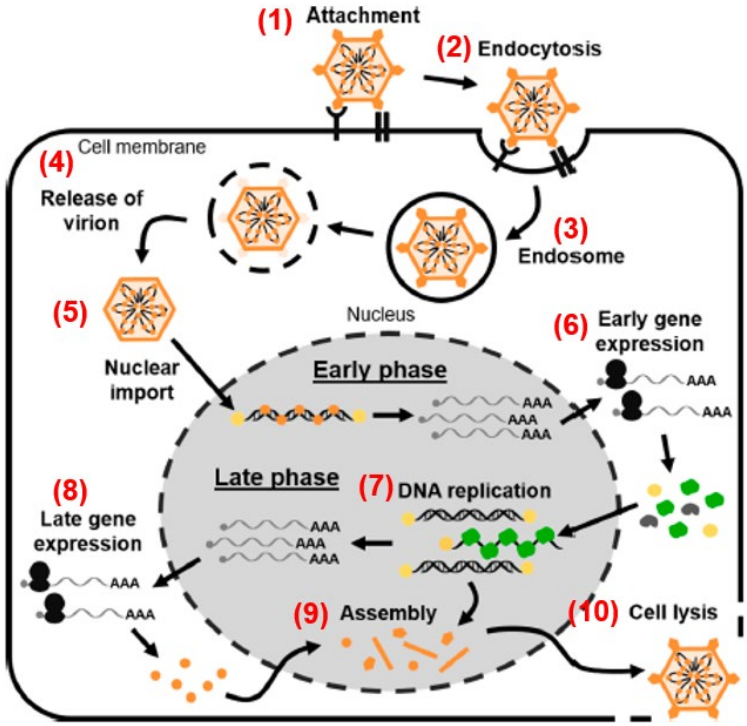

Figure 3: **Overview of the adenovirus replication cycle (Charman et al., 2019).**

3.4 Mutation and recombination of adenovirus

42. AdVs do not have the machinery for efficient integration into the host genome and therefore AdVs exhibit extremely low levels of integration i.e., integration is a rare event (Harui et al., 1999; Desfarges and Ciuffi, 2012; Hoppe et al., 2015; Dehghan et al., 2019). However, random integration of virus DNA into the host genome has been observed in rare cases (Harui et al., 1999; Stephen et al., 2008). AdV DNA is maintained as multiple episomal copies in the cytoplasm of infected cells (Harui et al., 1999).

43. Where a cell is infected by multiple HdAVs at the same time, exchange of genetic material can occur which promotes the molecular evolution of HAdVs through a process called homologous recombination. Homologous recombination appears to be restricted to members of the same species and occurs in the regions of high sequence homology (Lukashev et al., 2008). For instance, the comparison between DNA sequences among eight HAdV-C strains revealed 17 positions with nucleotide variations. However, only one of them altered the amino acid composition. Thus, it appears that HAdV-C accumulate predominantly neutral point mutations in their genomes that do not cause substantial modifications. This indicates a high-stability and conservation of protein sequence and may explain the relatively small number of HAdV-C serotypes.

44. Homologous recombination has been described in six HAdV species resulting in an increased number of members within those species (e.g., HAdV-B and HAdV-D). For example, bio-informatics analysis suggested that HAdV-4, a species E adenovirus like ChAd Y25, was a result of a recombination event between species B and C (Gruber et al., 1993).

45. Similarly, novel SAdVs have also been shown to arise by recombination (Ismail et al., 2018). There is 99.5% sequence homology between HAdV-B76 and Simian Adenovirus B35.1 (SAdV-B35.1) found in chimpanzee hosts and HAdV-4 also have 97% sequence homology to SAdV-E26 genome (Dehghan et al., 2013; Dehghan et al., 2019). Further, there is an evidence for possible cross-species transmission and genomic recombination between humans and chimpanzee hosts (Lasaro and Ertl, 2009; Roy et al., 2009; Wevers et al., 2011; Hoppe et al., 2015; Borkenhagen et al., 2019; Dehghan et al., 2019).

3.5 Epidemiology

3.5.1 Host range and transmissibility

46. ChAds have a limited host range and chimpanzees are the natural host (Bots and Hoeben, 2020). ChAds are not known to be pathogenic to any other animal species or plant cells (Wold and Toth, 2013). Experimentally, ChAds have been shown to infect mice, cotton rats, calves and humans when used at high concentrations.

47. ChAds are capable of infecting people as antibodies against ChAd have been detected in people exposed to chimpanzees and where hunting and butchering of nonhuman primates for food are widespread and eating bush meat is common. However, there is no evidence to indicate that people can pass on the virus to other people or animals (Xiang et al., 2006).

48. Transmission of AdVs from an infected individual is primarily via direct contact with conjunctival secretions, via inhalation of aerosols or via faecal-oral route (Allard and Vantarakis, 2017; Gray and Erdman, 2018; Khanal et al., 2018). The virus can also be spread indirectly via contact with infected articles e.g. handkerchiefs, linens or utensils contaminated by respiratory discharge from an infected person (Allard and Vantarakis, 2017).

3.5.2 Shedding

49. The predominant natural tropism of ChAd Y25 is respiratory and ocular (eye). ChAds were detected in the faeces of the healthy population of chimpanzees and other great apes present in the wild and in captivity (Roy et al., 2009; Tong et al., 2010; Wevers et al., 2011).

50. Following natural HAdV infection, virus particles are shed via respiratory or ocular secretions or in the faeces. Respiratory infections generate the highest viral load early post-infection with residual virus remaining for up to 2 months post-infection (Huh et al., 2019). The ease of transmission of AdV is thought to be facilitated by very high levels of viral particles shed into sputum or oral secretions of the infected person (Allard and Vantarakis, 2017).

51. HAdV shedding was also evaluated in faecal and oral swabs after oral administration of a live vaccine containing two HAdV serotypes (HAdV-4 and HAdV-7). Over 50% of the vaccine recipients tested positive for AdV faecal shedding between 7-28 days following vaccination. No faecal shedding was detected 28 days following vaccination or at any time point in throat swabs (Allard and Vantarakis, 2017).

3.5.3 Occurrence in the environment

52. ChAds and chimpanzees are not native to Australia. ChAd Y25 is not found in the natural ecosystem outside its natural host. Therefore, their occurrence is limited in Australia. However, HAdVs are ubiquitous in the environment and are widely distributed worldwide infecting humans.

53. HAdVs have been detected in various waters worldwide including wastewater, river water, drinking water, ocean and swimming pools (Allard and Vantarakis, 2017). HAdVs are more frequently

detected in high concentrations in domestic sewage and sludge in various countries and in some situations may be used in surveillance for faecal contamination (Allard and Vantarakis, 2017).

3.5.4 Control, environmental stability and decontamination methods

54. In otherwise healthy adults, infection with HAdV is generally asymptomatic or associated with mild disease and is generally managed through a combination of supportive care of the infected person and enhanced personal hygiene measures to limit transmission. Antiviral drugs may be used in immunocompromised patients or those with severe disease.

55. Despite the high prevalence of HAdV infection, there are currently no adenovirus-specific drugs that demonstrate efficacy as antiviral agents (Waye and Sing, 2010a; CDC - Adenoviruses, 2019). The antiviral agents commonly used in the first line adenoviral therapy are cidofovir and ribavirin (Waye and Sing, 2010a; CDC - Adenoviruses, 2019; Lion, 2019).

56. Generally AdVs are resistant to most chemical or physical decontamination processes and agents (including lipid-disrupting disinfectants) as well as high or low pH conditions (Rutala et al., 2006; Public Health Agency of Canada, 2014; Gray and Erdman, 2018). AdVs are also found to be resistant to UV radiation (Thompson et al., 2003; Thurston-Enriquez et al., 2003), thus supporting survival in treated wastewater and sewage, river, ocean and swimming pool water as well as drinking water (Public Health Agency of Canada, 2014).

57. AdVs as a group are very stable in the environment at pH 6-8 and below 40°C (Rexroad et al., 2006) and can survive for long periods in liquid or on surfaces in a desiccated state. For example, HAdV can survive up to 10 days on paper under ambient conditions and for 3-8 weeks on environmental surfaces at room temperature (Public Health Agency of Canada, 2014). Therefore, AdVs survival time depends on the relative humidity, temperature and on the type of surface (Abad et al., 1994).

58. AdVs are found to be sensitive to 70% ethanol, 0.9% Virkon S (>5 min contact time), 0.2% chlorine, 0.55% ortho-phthalaldehyde and 2.4% glutaraldehyde (McCormick and Maheshwari, 2004; Rutala et al., 2006). In addition, AdVs can be inactivated by heat e.g. heating to 56°C for 30 minutes or 60°C for 2 minutes or autoclaving (Public Health Agency of Canada, 2014; Allard and Vantarakis, 2017; Gray and Erdman, 2018).

Section 4 The GM vaccine - nature and effect of the genetic modification

59. The GM vaccine consists of a recombinant, replication defective virus, which has been modified to produce the SARS-CoV-2 spike glycoprotein. The GM vaccine is designed to provide protection from infection with SARS-CoV-2 which causes COVID-19 disease.

4.1 The genetic modifications

60. The GM vaccine was produced by deleting E1 and E3 genes from the ChAd Y25 genome and by replacing the E4 region open reading frame (Orf)4, Orf6 and Orf6/7 genes with equivalent genes from HAdV-5 into the same locus (Dicks et al., 2012). This results in a replication defective GMO which produces more virus yield during virus manufacture. In addition, a construct containing a human cytomegalovirus (CMV) promoter and codon-optimised full length SARS-CoV-2 spike gene fused to a human tissue plasminogen activator (tPA) leader sequence was then inserted into the E1 locus (van Doremalen et al., 2020c) to boost induction of an immune response.

61. The SARS-CoV-2 spike (S) protein consists of the receptor binding (S1) and membrane fusion (S2) domains. The S1 receptor binding domain has been shown to be responsible for host range and tropism (Huang et al., 2016; Li, 2016; Letko et al., 2020; Mousavizadeh and Ghasemi, 2020; Samrat et al., 2020). The receptor binding domain of the spike protein facilitates the virus attachment via angiotensin-converting enzyme 2 (ACE2) receptors present on human cells and fusion of virus and cell membranes, mediating the entry of SARS-CoV-2 into the target host cells. The role of the spike protein in receptor binding and entry into the host cells make the spike protein an attractive vaccine candidate and many

COVID-19 vaccines being developed have been based on this spike protein (Folegatti et al., 2020b; Logunov et al., 2020; Sadoff et al., 2020; Samrat et al., 2020; Zhu et al., 2020).

62. The GM vaccine was generated by inserting a gene encoding the SARS-CoV-2 S glycoprotein into the ChAdOx1 vaccine vector sequence. The process could be largely divided into three parts, deletion of E1 and E3 genes, modification of E4 gene and insertion of SARS-CoV-2 S gene.

4.1.1 Deletion of E1 and E3 genes

63. The E1 and E3 genes were deleted from the ChAd Y25 genome using the BAC vector (Dicks et al., 2012).

4.1.2 Modification of E4 gene

64. The E4 gene was modified by replacing ChAd Y25 native E4 Orf4, Orf6 and Orf6/7 genes with the equivalent genes from HAdV-5 (Dicks et al., 2012). Therefore, the resultant vector contains E4 Orf4, Orf6, Orf6/7 coding regions from HAdV-5 and the E4 Orf1, Orf2 and Orf3 coding regions from ChAd Y25 (Dicks et al., 2012). This vector was initially called ChAdY25-E and was later renamed to ChAdOx1.

4.1.3 Insertion of gene encoding SARS-CoV-2 spike protein

65. The full length sequence of the SARS-Cov-2 spike protein (GenBank accession number MN908947) was codon optimised to improve expression in human cells and the tPA leader sequence was fused upstream of the spike protein sequence. The sequence encoding both the spike protein and tPA was then cloned into an expression cassette containing a modified human CMV promoter with tetracycline operator sites and a poly-adenylation signal from bovine growth hormone. The expression cassette was then inserted into the E1 locus of the ChAdOx1 vector to generate the GM vaccine.

4.2 Effect of the genetic modification

66. Due to deletion of E1 and E3 genes, the resultant GMO is unable to replicate in the cells and unable to evade the host immune response.

67. Due to modification of the E4 gene, the GMO demonstrates increased virus yield i.e., allows efficient expression and growth of the virus in human cells during manufacturing of the GM vaccine.

68. Insertion of the gene encoding the full length SARS-CoV-2 spike protein in the ChAdOx1 vector was designed to induce antibodies against the SARS-CoV-2 virus in vaccinated people. The SARS-CoV-2 S glycoprotein is not toxic and does not confer any advantages to the adenoviral vector. Further, the antigen expression cassette does not alter the transmission route or host range of the ChAdOx1 vaccine vector.

69. As a result of these genetic modifications, the GMO cannot replicate in the host cells and will induce an immune response in humans but will not cause ill-health in humans.

4.3 Characterisation of the GMO

70. Data obtained from experiments and clinical trials using the proposed GMO and from other clinical trials using the same backbone/platform (ChAdOx1 vector) with different genes for a range of diseases has been used to describe the characteristics of the GMO.

4.3.1 Genetic stability and molecular characterisation

71. The ChAdOx1 vector has also been used in several clinical trials for testing against other human diseases, including the Middle Eastern Respiratory Syndrome (MERS) virus, a beta coronavirus that is related to SARS-CoV-2 (Antrobus et al., 2014; Coughlan et al., 2018; Folegatti et al., 2020a; Wilkie et al., 2020). The ChAdOx1 vector has been found to be genetically stable, safe and well tolerated in humans.

72. Further, studies have shown that the formation of replication competent ChAdOx1 during manufacture is very low due to differences in the E1 flanking sequence between HAdV-5 and ChAds (Tatsis and Ertl, 2004; Tatsis et al., 2006; Colloca et al., 2012; Ghebremedhin, 2014; Morris et al., 2016).

73. The sequence of the expression cassette for the SARS-CoV-2 S protein gene including the promoter and poly A regions were confirmed by DNA sequencing. DNA sequences for ChAdOx1 (NCBI reference sequence: txid1123958) and spike protein are available in GenBank (NCBI reference sequence: YP_009724390.1; GenBank accession number MN908947.3).

74. The GM vaccine does not contain a selectable marker, however the GMO can be distinguished from the ChAd Y25 virus (parent strain) or SARS-CoV-2 using a specific PCR test. These genetic markers include the tPA leader sequence inserted into the SARS-CoV-2 S protein sequence, the absence of E1 and E3 genes, and modified E4 gene.

75. The applicant has stated that the GMO will be routinely monitored during manufacturing to ensure the virus has not gained replication competency. Thus, each vaccine batch will be subjected to a number of tests to ensure consistency and quality of the manufactured product. Vaccine quality will be assessed by TGA. Further, the genetic stability of the GMO will be also examined to confirm the presence of the full genomic sequence.

76. The use of the BAC vector in the generation of the GMO allows stable incorporation of gene sequences and improves genetic stability to the virus (Dicks et al., 2012).

77. Adenoviral vectors (including ChAdOx1 vector) are considered non-integrating vectors which do not have a propensity to integrate or reactivate in a host (EMEA, 2007; FDA, 2020).

4.3.2 Biodistribution and shedding of the GMO

78. Biodistribution studies with this GMO have not been conducted. However biodistribution data from similar, replication incompetent ChAd-based vaccines (AdCh63-ME-TRAP and AdCh63-MSP-1 for malaria, AdCh3NSmut for hepatitis C and ChAd155-RG) showed limited spread to the draining lymph node and no other spread beyond the immediate site of injection following intramuscular injection in mice and rats (BE/20/BVW2, 2020; Napolitano et al., 2020).

79. Similarly, local administration (intranasal, intrabroncheal, intramyocardial, intramuscular or intratumoural injection) of replication defective HAdV-5 and HAdV-35 (E1 and E3 genes deleted) in rabbits and humans showed negligible virus shedding in pharyngeal, rectal, nasal swabs, urine and blood samples (Crystal et al., 2002; Sheets et al., 2008; Wold and Toth, 2013). In addition, no recombinant competent virus was detected in the analysed samples, suggesting that no homologous recombination was occurring with other AdVs.

80. A small number of studies with other replication deficient adenoviral vectors have reported shedding of vector DNA or infectious particles, while many others have not detected any shedding (Schenk-Braat et al., 2007). In general, shedding of replication defective adenoviral vectors is considered to be a rare event (Wold and Toth, 2013). Shedding is dependent on the route of administration, site of administration, type of samples analysed and length of time after administration. For instance, shedding of chimpanzee adenoviral based vaccine PanAd3-RSV (E1 and E4 deleted) was studied in a Phase I clinical study following intramuscular or intra-nasal administration (Green et al., 2015). Urine and throat swabs from 40 subjects were collected 3 days following intramuscular vaccination, and viral shedding was evaluated using a specific PCR test. The results were negative for all samples, demonstrating that there was no detectable shedding of the vaccine following intramuscular administration by 72 hours post administration. Similarly, nasal samples collected 3 days after intranasal administration of PanAd3-RSV did not detect any viral shedding (Green et al., 2015).

81. The GMOs inability to replicate prevents its dissemination in the vaccinated person. Taken into consideration the above mentioned biodistribution and shedding data from replication incompetent adenoviral based vaccines, the GMO is expected to be confined to the intra-muscular injection site and the draining lymph nodes of the human host and no virus excretion is expected with the GMO. Thus, there is no evidence to suggest that the GMO would be present in the environment from shedding following vaccination of people.

4.3.3 Stability in the environment and decontamination

82. The stability of this GMO in the environment (surfaces, water types and sediments) has not been tested. Other recombinant AdVs (AdV expressing GFP) have been shown to have reduced capacity to survive in fresh surface water, cold water and dark sediments compared to wild-type AdVs (Rigotto et al., 2011; Elmahdy et al., 2018). It is likely that, with regard to environmental stability, this GMO will be similar to or have reduced survival than wild-type AdVs (see Chapter 1, Section 3.5.4). Further since the GMO is replication incompetent, it is not possible for the GMO to multiply and spread in the environment and any initial GM vaccine would be degraded over time.

83. Methods of decontamination effective against the parent organism, ChAd Y25, are expected to be equally effective against the GMO (see Chapter 1, Section 3.5.4).

4.3.4 Non-clinical studies

84. Pre-clinical studies with the GM vaccine in mice, pigs and rhesus macaques have shown a good safety profile and the ability of the vaccine to elicit both neutralising antibody and T-cell responses following a single or homologous prime-boost regime (Graham et al., 2020; van Doremalen et al., 2020b). Further, the vaccine protected SAR-CoV-2 infected rhesus macaques from viral pneumonia and immune-enhanced inflammatory disease. In addition, no infectious virus particles were detected in the lungs and intestinal tissues of these infected animals (van Doremalen et al., 2020b). Whilst a single dose of GMO induced antigen-specific antibody and T cell responses in mice and pigs, a booster immunisation enhanced antibody responses, particularly in pigs and significantly increased SARS-CoV-2 neutralising antibody titres (Graham-2020).

4.3.5 Safety and immunogenicity in clinical studies

85. A phase 1/2 clinical trial with the GMO has been completed. The GM vaccine was found to be safe, well tolerated and elicited immune response in 543 vaccinated individuals aged 18-55 years (Folegatti et al., 2020c). However, protection against SARS-CoV-2 in humans was not examined in this study. The most common side effects following vaccination were pain, redness, swelling, itching at the site of injection and fever, malaise, fatigue, headache, vomiting, joint pain and muscle ache. No serious adverse events were observed in this study (Folegatti et al., 2020b).

86. Similarly, an ongoing Phase 2/3 clinical trial demonstrated that the GM vaccine is safe and well tolerated in both older adults (56-69 years and 70 years and older) and younger adults (18-55 years) after prime-only and prime-boost vaccination (Ramasamy et al., 2020). Further, immune responses were induced in all age groups and were boosted and maintained at 28 days after booster vaccination. The adverse events reported reflected those observed in the phase 1/2 clinical trial with reactions overall less common in older adults compared to younger adults. In this study, 13 serious adverse events were reported but none of them were considered to be related to the GM vaccine.

87. The interim analysis of four clinical trials in Brazil, South Africa and the UK showed that the GM vaccine is safe and efficacious against symptomatic COVID-19 with prime-boost vaccination (Voysey et al., 2020). The efficacy of the GM vaccine in individuals who received two standard doses was 62.1% whereas efficacy was 90% in individuals who received first low dose and a second standard dose. Overall, the GM vaccine showed efficacy of 70.4% in vaccinated individuals across both groups. In this study, 175 serious adverse events occurred in 168 vaccinated individuals, where 84 events were reported in the GM vaccine group and 91 events in the control group.

Section 5 The receiving environment

88. The receiving environment forms part of the context for assessing risks associated with import, transport, storage and disposal of the GM vaccine (OGTR, 2013). It informs the consideration of potential exposure pathways, including the likelihood of the GMO spreading or persisting outside the site of release.

5.1 Site of vaccination

89. The intended primary receiving environment would be the muscles (at the site of injection) of the vaccine recipient as the GM vaccine will be delivered via intramuscular injection by a trained healthcare professional in vaccination sites.

90. The secondary receiving environment would be the clinical facility/vaccination site where the vaccine is prepared and administered. Most vaccination facilities/sites would be equipped to deal with scheduled drugs and infectious agents. They are required to comply with *AS/AZS 2243.3:2010 Safety in laboratories – Microbiological Safety and Containment* (Standards Australia/New Zealand 2010).

91. The principal route by which the GMO may enter the wider environment following vaccination is via shedding. However, as the injection of non-replicating GMO is via intramuscular injection, wide spread shedding is not expected due to localisation of viral particles at the injection site and draining lymph nodes. Further, GMO may also enter the environment via accidental spilling of unused vaccine.

5.2 Presence of related viral species in the receiving environment

92. The presence of related viruses may offer an opportunity for introduced genetic material to transfer between the GMO and other organisms in receiving environment.

93. AdVs belong to five genera: *Aviadenoviruses* (infecting birds), *Mastadenovirus* (infecting mammals), *Atadenovirus* (infecting a broad range of hosts including reptiles, lizards and some mammals), *Siadenovirus* (infecting one species of frog and tortoise and multiple species of domestic, wild and captive birds) and *Ichtadenovirus* (infecting fish) (Tong et al., 2010; Lange et al., 2019; Vaz et al., 2020). As such, they are a common cause of infection in animals and humans of all ages and can be found in all environments where humans or animals congregate in groups (Usman N, 2020). A more detailed description of AdVs presence in the environment is in Section 3.5.3.

94. As chimpanzees are not native to Australia, the presence of ChAds is expected to be very limited in the Australian environment.

5.3 Presence of similar genetic material in the environment

95. The balance of a system could be perturbed by the introduction of new genetic material through horizontal gene transfer or through release of GMO into the environment. However, the effect of perturbation would be relatively small if the genetic material was already present in the system and did not confer any selective advantage to an organism that gained this genetic material.

96. All of the genes in the GMO would be functionally similar to ones present in the naturally occurring SARS-CoV-2 virus. The genes introduced into the GMO were derived from the naturally occurring SARS-CoV-2 virus and so similar genetic material would already be present in the environment, as evidenced through detection in wastewater.

Section 6 Previous authorisations

97. The GM vaccine has not been previously authorised for commercial supply in any region or country.

98. There are currently 6 clinical trials (NCT04324606, NCT04400838, NCT04536051, NCT04444674, NCT04516746 and NCT04540393) ongoing to test the safety, immunogenicity, and efficacy of GM vaccine in different countries (the UK, the United States (US), Brazil, South Africa, Argentina, Chile, Colombia, Japan, Peru and the Russian Federation) for the prevention of COVID-19.

99. The initial importation, transport, supply, storage and disposal of the GM Master vaccine seed into Australia and dealings involving quality control sampling and batch release testing is covered under Notifiable low risk dealing approval (NLRDs) held by AstraZeneca.

100. The Regulator has recently approved DNIR licences (DNIR-630 and DNIR-632) to manufacture, supply frozen bulk drug substance, formulate and fill/finish the GM vaccine as part of the overall program for the supply of recombinant antigen for the prevention of COVID-19 in Australia.

Chapter 2 Risk assessment

Section 1 Introduction

101. The risk assessment identifies and characterises risks to the health and safety of people or to the environment from dealings with GMOs, posed by or as the result of gene technology (Figure 4). Risks are identified within the established risk assessment context (Chapter 1), taking into account current scientific and technical knowledge. A consideration of uncertainty, in particular knowledge gaps, occurs throughout the risk assessment process.

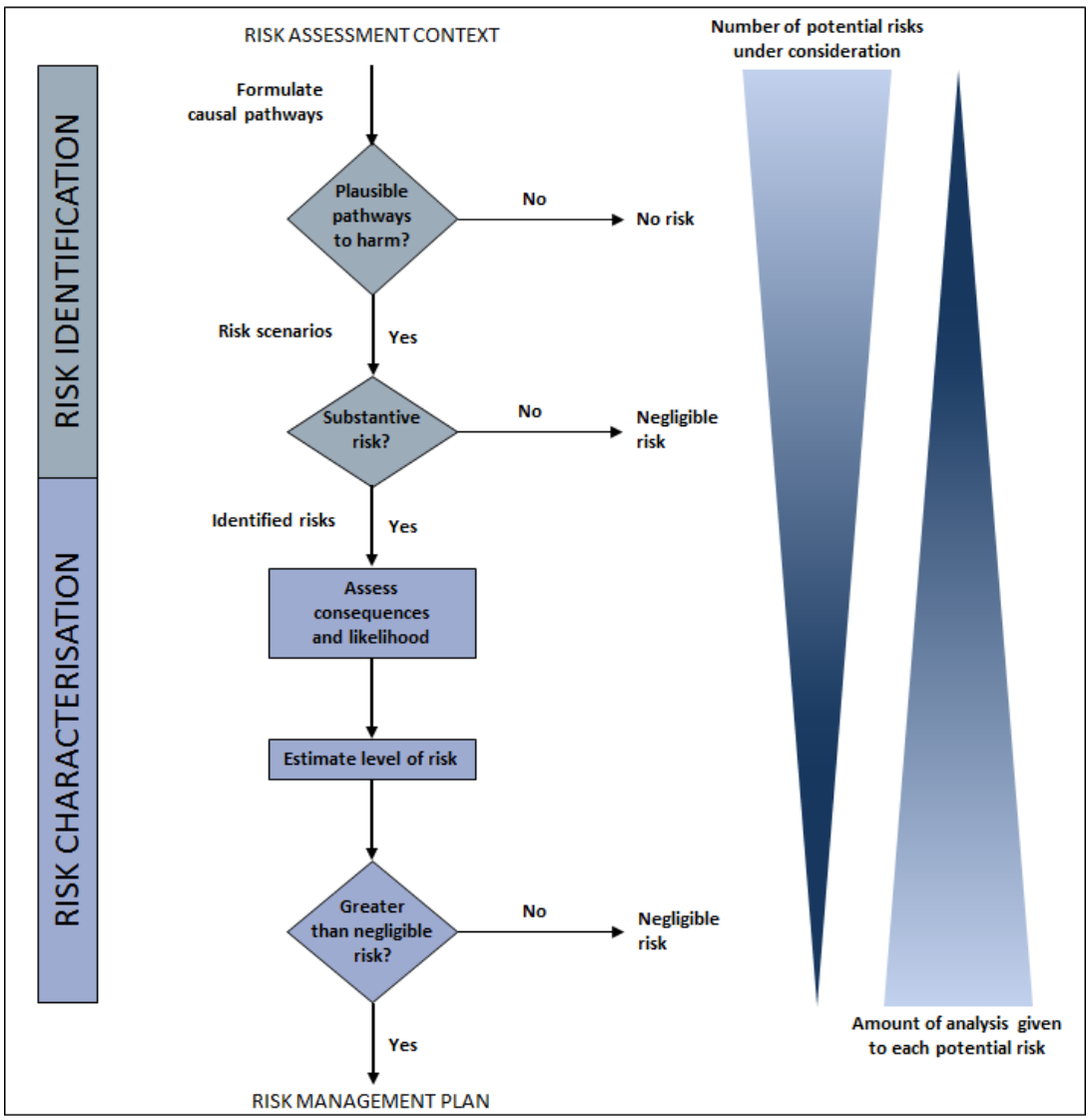

Figure 4: **The risk assessment process**

102. The Regulator uses a number of techniques to identify risks, including checklists, brainstorming, previous agency experience, reported international experience and consultation (OGTR, 2013).

103. Risk identification first considers a wide range of circumstances in which the GMO, or the introduced genetic material, could come into contact with people or the environment. This leads to postulating causal pathways that may give rise to harm for people or the environment from dealings with a GMO. These are called risk scenarios.

104. Risk scenarios are screened to identify substantive risks, which are risk scenarios that are considered to have some reasonable chance of causing harm. Risk scenarios that could not plausibly occur, or do not lead to harm in the short and long term, do not advance in the risk assessment process (Figure 4), i.e. the risk is considered no greater than negligible.

105. Risk scenarios identified as substantive risks are further characterised in terms of the potential seriousness of harm (Consequence assessment) and the likelihood of harm (Likelihood assessment). The consequence and likelihood assessments are combined to estimate the level of risk and determine whether risk treatment measures are required. The potential for interactions between risks is also considered.

Section 2 Risk identification

106. Postulated hypothetical risk scenarios are comprised of three components (Figure 5):

i. The source of potential harm (risk source)

ii. A plausible causal linkage to potential harm (causal pathway), and

iii. Potential harm to people or the environment.

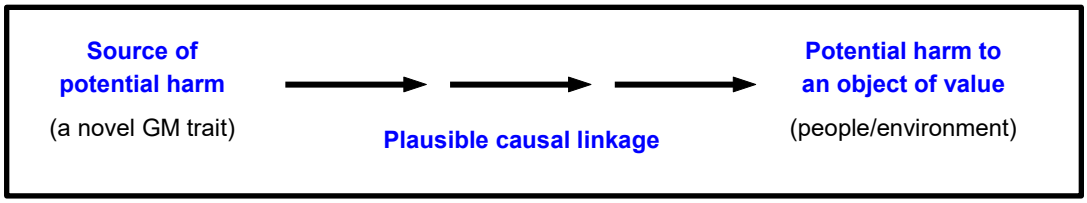

Figure 5: **Components of a risk scenario**

107. When postulating relevant risk scenarios, the risk context is taken into account, including the following factors detailed in Chapter 1:

- the proposed dealings
- the proposed limits including the extent and scale of the proposed dealings
- the proposed controls to limit the spread and persistence of the GMO and
- the characteristics of the parent organism(s).

2.1 Risk source

108. The parent organism of the GMO is the chimpanzee adenovirus isolate Y25 (ChAd Y25). Details of the pathogenicity and transmissibility of ChAd is discussed in Chapter 1. Infection is generally the result of inhalation of aerosol droplets excreted from respiratory or ocular secretions containing the virus or of mucosal exposure to the virus or via faecal-oral transmission. ChAd infects chimpanzees and causes common cold-like symptoms, bladder infections or diarrhoea.

109. Toxicity and allergenicity of the introduced genes and their protein products have not been directly considered, but are taken into account in the context of their contribution to ill health.

110. Potential sources of harm can be due to the intended novel GM traits associated with one or more introduced genetic elements, or unintended effects/traits arising from the use of gene technology. Unintended effects can arise through a horizontal gene transfer (HGT) which is the stable transfer of genetic material from one organism to another without sexual reproduction. All genes within an organism, including those introduced by gene technology, can be transferred to another organism by HGT. A gene transferred through HGT could confer a novel trait to the recipient organism. The novel trait may result in negative, neutral or positive effects on the fitness of the recipient organism. HGT commonly occurs from cells to viruses but rarely occurs from viruses to their

host cells, with the exception of retroviruses and some DNA viruses. This pathway is further considered as a potential source of risk.

111. As discussed in Chapter 1, Section 4.1, the GMO has been modified by the deletion of E1 and E3 genes, by modifying the E4 gene and by insertion of gene encoding a codon-optimised full length SARS-CoV-2 spike protein. These introduced genes and their encoded proteins are considered further as a potential source of risk.

2.2 Causal pathway

112. The following factors are taken into account when postulating possible causal pathways to potential harm:

- the proposed dealings, which are import, transport or disposal of the GMO and possession (including storage) in the course of any of these dealings,
- restrictions placed on the import, transport or disposal of the GMO by other regulatory agencies, the States and Territories,
- characteristics of the parent organism,
- routes of exposure to the GMOs, the introduced gene(s) and gene product(s),
- potential effects of the introduced gene(s) and gene product(s) on the properties of the organism,
- potential exposure of other organisms to the introduced gene(s) and gene product(s) from other sources in the environment,
- potential exposure of other organisms to the GMOs in the environment,
- the release environment,
- spread and persistence of the GMOs (e.g. dispersal pathways and establishment potential),
- environmental stability of the organism (tolerance to temperature, UV irradiation and humidity),
- gene transfer by horizontal gene transfer,
- unauthorised activities, and
- practices before and after administration of the GMO.

113. The TGA regulates quality, safety and efficacy of the GM vaccine (i.e., GMO) under the *Therapeutic Goods Act 1989*, as mentioned in Chapter 1, Section 1.1. This includes:

- assessment of patient safety, vaccine quality and efficacy prior to inclusion on the ARTG,
- recommended practices for the transport, storage and disposal of the GM vaccine under the *Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8,*
- requirements for the scheduling, labelling and packaging under the *Poisons Standard.*

114. The current assessment focuses on risks posed to people other than the intended vaccine recipient, and to the environment, including long term persistence of the GMOs, which may arise from the import, transport, storage or disposal of the GMO.

115. The Act provides for substantial penalties for unauthorised dealings with GMOs or non-compliance with licence conditions, and also requires the Regulator to have regard to the suitability of an applicant to hold a licence prior to the issuing of the licence. These legislative provisions are considered sufficient to minimise risks from unauthorised activities. Therefore, unauthorised activities will not be considered further.

116. As discussed in Chapter 1, Section 4.3.2, the ChAd-based viral vectors were found to be localised to the site of injection and draining lymph nodes after intramuscular injection. Further, no virus shedding was detected with ChAd-based and HAdV-based viral vectors. Therefore, the GMO is

expected to be confined to the intramuscular injection site and the draining lymph nodes of the vaccine recipients and no virus shedding is expected with the GMO from the vaccine recipients resulting in release of the GMO in the environment. Thus, there is no potential risk of the GMO to be shed from the vaccine recipients and therefore, this risk scenario will not be considered further.

117. Infection with AdV can result in latent infection in lymphoid tissues and increase the period of viral persistence in the body. However, the AdV remains episomal throughout the infection and does not integrate into the host DNA. Further, adenoviral vectors (including ChAdOx1 vector) have been used extensively in clinical studies as a vaccine and gene therapy for almost 30 years (Crystal, 2014) and there is no evidence of integration of viral DNA into the host genome. These are considered non-integrating vectors which do not have a propensity to integrate or reactivate in a host (EMEA, 2007; FDA, 2020). Thus, the consequences of integration of viral DNA into a host cell genome will not be further discussed.

2.3 Potential harms

118. The following factors are taken into account when postulating relevant hypothetical risk scenarios for this licence application:

- harm to the health of people or desirable organisms, including disease in humans or animals or adverse immune response
- the potential for establishment of a novel virus in the environment

2.4 Postulated risk scenarios

119. Three risk scenarios were postulated and screened to identify substantive risk. These hypothetical scenarios are summarised in Table 1 and discussed in depth in this section 2.4.1-2.4.3 (this chapter).

120. In the context of the activities proposed by the applicant and considering both the short and long term, none of the three hypothetical risk scenarios gave rise to any substantive risks that could be greater than negligible.

Table 1 Summary of hypothetical risk scenarios from dealings with GM vaccine

Risk scenario	Risk source	Potential causal pathway	Potential harm	Substantive risk	Reason
1	GMO	Exposure of other people and animals to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes during (a) Preparation and administration of the GMO (b) Import, transport or storage of the GMO (c) Disposal of the GMO ⬇ Transduction of cells by GMO ⬇ Expression of the spike protein	Adverse immune reactions (e.g., cytokine storm)	No	• The GMO is replication incompetent. GMO will not produce further viral particles to sustain an infection. • Any reactions to the spike protein would be transient and rapidly cleared by the immune system. • GMO has showed good safety profile. • The dose received through accidental exposure would be far smaller than that administered during vaccination and would not be sufficient for immunisation of exposed persons.

Risk scenario	Risk source	Potential causal pathway	Potential harm	Substantive risk	Reason
					• Import, transport, storage and disposal will follow the well established procedures.
2	GMO	Exposure of other people and animals to the GMO as mentioned in Risk Scenario 1 ⬇ Transduction of cells by GMO ⬇ Transduced cells co-infected with AdV ⬇ (a) Complementation of E1 by AdV (b) Homologous recombination with AdV ⬇ (a) Production of more replication incompetent ChAdOx1 with spike protein (b) Formation of replication defective AdV expressing spike protein; **OR** Replication competent GMO without spike protein	Adverse immune reactions (e.g., cytokine storm) Disease in people or animals	No	• There is a low probability of both GMO and AdV infecting the same cell at the same time. • A large proportion of the population have a pre-existing immunity to HAdV reducing the likelihood of HAdV infection. • There is a low probability of continuous complementation of GMO by AdV because AdV infection is self-limiting. • Recombination among adenoviruses is restricted to the same species. • There is low homology between E1 flanking regions of GMO and HAdVs. Site-directed recombination was used to insert the transgene into E1 gene of GMO further decreasing the likelihood of recombination with HAdV. • Natural occurring homologues (wild-type ChAdV) are only known to circulate in chimpanzees. ChAd is not known to cause disease in humans and other animals.
3	GMO	GMO release into the environment (e.g. sewerage, spills) ⬇ Exposure to people or animals ⬇ As per scenario 1-2	Adverse immune reactions (e.g. cytokine storm); Disease in people or animals	No	• As discussed in Risk Scenario 1 and 2. • Chimpanzees are the only natural hosts to ChAds. Chimpanzees are not native to Australia and would only be found in zoos. No other animals are expected to be infected with ChAds. • GMO does not infect aquatic species. GMO cannot persist and replicate inside and outside the host, hence GMO is unable to maintain a

Risk scenario	Risk source	Potential causal pathway	Potential harm	Substantive risk	Reason
					stable presence in the environment for long periods.

2.4.1 Risk scenario 1

Risk source	GMO
Potential causal pathway	Exposure of other people and animals to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes during (a) Preparation and administration of the GMO (b) Import, transport or storage of the GMO (c) Disposal of the GMO ⬇ Transduction of cells by GMO ⬇ Expression of the spike protein
Potential harm	Adverse immune reactions (e.g., cytokine storm)

Risk source

121. The source of potential harm for this postulated risk scenario is the GMO.

Potential causal Pathway

122. People (person handling the GMO) and animals could be directly or indirectly exposed to the GMO in a number of ways. The GMO could be transmitted via aerosol droplets generated during an unintentional spill of the GMO and preparation of the GMO. It could also be transmitted when contaminated surfaces, such as hands or tissues, make contact with mucous membrane and via needle stick injury. This exposure could result in infection with the GMO that could lead to ill health.

Exposure during preparation and administration of the GMO

123. As discussed in Chapter 1, Section 2.1, the GMO would be distributed via vaccination facilities/sites. There is the potential for exposure of people involved in the administration of the GM vaccine by needle stick/sharps injury, aerosols formation during preparation and/or due to breakage/spillage of GM vaccine onto surfaces during preparation and administration.

124. The GMO would be prepared and administered by authorised, experienced and trained medical staff. All personnel working in settings where healthcare is provided, including vaccination services, are required to comply with the standard precautions for working with potentially infectious material, as described in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019).* Compliance with these behavioural practices at vaccination sites will limit and control unintended exposure of people to the GMO.

125. Caregivers and healthcare personnel who come into close contact with vaccinated people may be inadvertently exposed to the GMO during administration. Caregivers and others exposed to the GM vaccine in this way would only be expected to be exposed to low levels of the GMO and this is not expected to result in any negative effects or ill-health. Furthermore, formation of replication-competent adenovirus or presence of the vector in healthcare personnel who came in close contact with the patients have not been observed in studies which looked into these parameters (Schenk-Braat et al., 2007).

126. The above mentioned controls would minimise the potential exposure of people to the GMOs during administration of the GMO.

Exposure during import, transport and storage of the GMO

127. If the GM vaccine was unintentionally/accidentally spilled or lost during import, transport or storage, this could result in exposure to people or animals in the area, as aerosol droplets could be formed, leading to aerosol or liquid contact with eyes or mucous membranes/skin. Further, people or animals could be inadvertently exposed to the GMO via contact with materials or surfaces contaminated with the GMO through subsequent hand to mouth transmission. This could result in infection with the GMO.

128. The applicant proposes to import the GMO from overseas as a multi-dose vial. These vials would be packaged in secondary cartons and the cartons packed in shipping cartons for distribution (Chapter 1, Section 2.1). Transport of GMO between the port of entry and the warehouse would continue in this packaging. This would lower the likelihood of unintended dispersal of the GMOs.

129. Similarly, the GMO manufactured within Australia will also be supplied as a multi-dose vial and these vials would also be packaged into secondary cartons followed by shipping boxes. This would reduce the chances of accidental dispersal of the GMOs.

130. Vaccines are classified as Schedule 4 medicines. Therefore, storage, handling and transport would be in accordance with *the Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8 (NCCTG 2011) and the WHO's Good Distribution Practices for pharmaceutical products (*WHO 2010). These practices would minimise the chances of damaged and leaking stock going unnoticed and increase the chances of GM vaccine being handled by individuals who would know how to decontaminate a spill, thus minimising the probability of unintended dispersal of the GMOs.

131. Additionally, the GM vaccine will be transported and stored according to the *National Vaccine Storage Guidelines: Strive for 5* (Department of Health, 2019) and the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2020). The cold chain, which is intended to preserve the potency of the vaccine, requires cold packaging/refrigeration and this adds a level of containment during import, storage and transport.

132. The GMO may cause mild disease in chimpanzees and other great apes but is not expected to cause any disease in humans and other animals. Therefore, the risk of exposure to the GMO resulting in disease in other people and animals is very low. Further, the exposure to animals during import, transport and storage is highly unlikely unless the spill occurs outside the premises/shipping containers.

133. The applicant proposes that the people involved in the import, transport and storage of the GM vaccine will have access to the material safety data sheet (MSDS). The MSDS would provide procedures to implement in response to a spill where any spilled/residual GMO would be quickly inactivated with a suitable disinfectant effective against the GMO. Therefore, the consequence of an accidental spill during import, transport and storage would be minimised by implementing spill clean-up procedures that would kill the GMO.

134. The import, transport and storage procedures proposed by the applicant meet the requirements of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* and would mitigate exposure due to spills of the GMO during these dealings.

Exposure during disposal of the GMO

135. Individuals may be inadvertently exposed to GMOs while disposing of used, expired, or unused vials of the GM vaccine. The two locations where this is most likely to occur are at:

- distribution warehouses where stocks of the GM vaccine are held

- locations where the GM vaccine is administered.

136. The *Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8* (NCCTG 2011) requires:

- specific training for personnel handling medicines that pose high risk to personnel if package integrity is breached or spillage occurs
- waste medicines be collected and destroyed by a person who is licensed or permitted to do so under relevant State or Territory legislation
- medicines for destruction be enclosed in sealed packaging or in a container.

137. The unused and expired vials of the GMO as well as the vials with residual GMO, syringes and waste contaminated with the GMO would be treated as clinical/medical waste and disposed of in accordance with the waste disposal methods approved by the Environmental Protection Agency or Health Department in the relevant State or Territory (TAS, 2007; NT, 2014; WA, 2016; ACT, 2017; NSW, 2018; QLD, 2019; SA, 2020; VIC, 2020). Adherence with these procedures would reduce the likelihood of accidental exposure of people or animals to the GMO.

138. For productive infection to occur, individuals must be exposed to an infectious dose. Residual liquid in used vials and used syringes would not contain a sufficient titre to cause productive infection. The same would apply to secondary waste such as gloves that may be contaminated with the GMO. The GMO is unable to replicate inside and outside the host, so viruses in the used vials could not multiply to reach an infective dose. Thus, the dose received through accidental exposure would be far smaller than that administered during vaccination. Therefore, even if an individual or animal is inadvertently exposed to the GMOs, they are unlikely to develop disease.

139. Taken together, these proposed disposal and decontamination procedures would minimise and control risks associated with conducting these dealings with the GMOs.

Potential harm

140. If people or animals are exposed to the GMOs, they could develop flu-like symptoms or local inflammation for a short period of time before the virus is cleared by the immune system. It is highly unlikely that exposed people or animals would experience adverse immune responses and severe illness following exposure, as the GMO does not cause disease in humans or animals other than great apes.

141. As the GMO is replication incompetent, it is unable to produce further viral particles which are required to sustain an infection. In addition, any reactions to the spike protein would be transient and the GMO would be rapidly cleared by the immune system. The minimal exposure and transient nature of infection would be expected to result in very mild, or negligible symptoms and would also minimise the potential for an adverse immune response to the GMO. Therefore, exposure to the GMO is not expected to result in an infection and would not result in an increased disease burden in humans or animals.

142. As mentioned in Chapter 1, Section 4.1, the SARS-CoV-2 virus enters a host's cells via the ACE2 receptor, which is involved in the renin-angiotensin-aldosterone system. When exposed to ChAdOx1 nCov-19, there is a possibility that the spike proteins produced will bind to ACE2, which can then prevent the conversion of angiotensin II into angiotensin. These could result in more angiotensin II binding to the ATI1 receptor, which can lead to detrimental effects such as vasoconstriction and enhanced inflammation and/or increased angiotensin II expression in the lungs. However, there has not been any reported cases of such effects. Further, it is very unlikely that the amount of spike protein present in the replicative defective viral vectored vaccine can have a sustained effect on people. To date, vaccines that have used the spike proteins from SARS-CoV-2 have shown a good clinical safety profile (Folegatti et al., 2020b; Logunov et al., 2020; Ramasamy et al., 2020; Sadoff et al., 2020; Voysey et al.; Zhu et al., 2020).

143. Vaccines against SARS-CoV-2 using the full length spike protein in replicative defective viral vectors including ChAdOx1 based vaccine have shown the ability to generate neutralising antibodies against SARS-CoV-2 (Folegatti et al., 2020b; Logunov et al., 2020; Ramasamy et al., 2020; Sadoff et al., 2020; Voysey et al.; Zhu et al., 2020). There is potential for these vaccines to cause antibody-dependant enhancement[2]-mediated viral entry or immunopathology via the generation of sub- or non-neutralising antibodies towards the spike protein (Arvin et al., 2020; Su et al., 2020). However, there has not been any reports of antibody-dependant enhancement (ADE) associated with these COVID-19 vaccine candidates to date. The administration of convalescent plasma from patients who had recovered from SARS-CoV-2 infection into 20,000 patients who had a high risk of severe COVID-19 disease showed low incidence of serious adverse events (Joyner et al., 2020). Further, no ADE was observed with inactivated-whole SARS-CoV-1 (Luo et al., 2018), DNA vaccine expressing SARS-CoV-2 S protein (Arvin et al., 2020) and ChAdOx1 MERS (van Doremalen et al., 2020a) in rhesus macaques upon re-infection. To date, there is no conclusive evidence demonstrating a risk of ADE in humans in relation to SARS-CoV-2 infection.

Conclusion

144. The potential for an unintentional exposure of people and animals to the GMO resulting in increased disease burden in humans and animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further detailed assessment.

2.4.2 Risk Scenario 2

Risk source	GMO
Potential causal pathway	Exposure of other people and animals to the GMO as mentioned in Risk Scenario 1 ⬇ Transduction of cells by GMO ⬇ Transduced cells co-infected with AdV ↙ ↘ Complementation of E1 by AdV → ⬇ → Production of more replication incompetent GMOs Homologous recombination with AdV → ⬇ → Formation of replication defective AdV expressing spike protein **OR** Replication competent GMO without spike protein
Potential harm	Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals

Risk source

145. The source of potential harm for this postulated risk scenario is the GMO.

[2] Antibody-dependant enhancement can occur when pre-existing sub- or non-neutralising antibodies towards a virus can enhance the viral entry into host's cells during secondary viral infections. This antibody-dependant enhancement mediated viral entry has been mostly documented in flaviviruses (e.g. dengue virus) but also observed in various viral infections such as HIV, Ebola and coronaviruses (e.g. MERS and SARS-CoV-1).

Potential causal Pathway

146. The transmission of GMO could occur by the pathways mentioned in Risk Scenario 1 which could potentially result in transduction of host cells at the exposed area. If the person or animal exposed to the GMO has an existing infection of AdVs at the same time of exposure or acquired an AdV infection while the GMO is present, this co-infection could potentially result in complementation and recombination of the GMO causing adverse immune reactions.

Complementation of E1 by AdV

147. The GMO could regain the ability to replicate in the host cells via transient complementation of E1 gene by AdVs. For complementation to occur, the person or animal exposed to the GMO would also need to be infected with an AdV (either ChAd or HAdV) at the same time and in the same cell. This could result in the production of more replication incompetent GMOs.

148. ChAds only circulate in chimpanzees and chimpanzees are not native to Australia. Therefore, the co-infection with the wild-type ChAds occurring at the same time and in the same cell in humans or animals is highly unlikely.

149. HAdV infects over 80% of the human population, therefore, there is a possibility for a GMO exposed person to acquire HAdV infection and which could provide E1 gene in *trans* for complementation to occur. This could result in the multiplication of GMOs in the host.

150. ChAds and HAdV-5 share a close homology (94% similarity) in their genome (Morris et al., 2016; Bots and Hoeben, 2020). This could allow the E1 gene from a HAdV-5 infected person to complement the missing E1 gene in the GMO. Therefore, it is possible that co-infection of HAdV-5 and GMO in the same cells could result in the production of more GMOs in the host. However, a large proportion of the population already have a pre-existing immunity to HAdV-5 which reduces the likelihood of HAdV-5 re-infection. In addition, there is a low probability of continuous complementation of GMO by HAdV-5 as HAdV-5 infection is self-limiting (Lichtenstein and Wold, 2004). Thus, this reduces the chances of co-infection in the host and eventual production of more GMOs in the host.

151. Studies have demonstrated that other HAdVs (except ChAd and HAdV-5) are incapable of replicating in cell lines that express E1 gene from HAdV-5 (Kovesdi and Hedley, 2010). This data suggests that HAdVs could only replicate in permissive cells which provide the essential viral replication E1 gene in trans i.e., requires serotype specific provision of E1 gene for complementation. Therefore, even if co-infection with other HAdVs and the GMO were to occur in the same cell, the GMO would still be unable to multiply in the host and would not increase the number of GMOs in the host.

Homologous recombination with AdV

152. Similar to complementation, homologous recombination also requires the person or animal exposed to the GMO to be infected with a wild-type AdV (either ChAd or HAdV) at the same time. This co-infection and recombination process could result in the generation of two different GM recombinants. These GM recombinants could contain either the gene encoding S protein or E1 gene due to co-localisation of these genes in the GMO genome and the packaging constraints on the virus genome size. Firstly, the wild-type AdV could receive the spike protein gene from the GMO and gain immuno-stimulatory function. Secondly, the GMO could regain its E1 gene but lose the gene encoding spike protein and become replication competent. These new viruses could then be shed from the host and transmitted to other hosts in the environment.

153. A recombinant virus generated due to homologous recombination could alter the characteristics (e.g., pathogenicity, host range, tissue tropism, latency, and infectivity) of the GMO. However, homologous recombination is unlikely to expand the host range beyond humans or chimpanzees (Rogers et al., 2020).

154. As discussed Chapter 1, Section 3.4, recombination between adenoviruses is rare and is restricted to the same species (Lukashev et al., 2008). For a homologous recombination to occur, a GMO exposed person or chimpanzee is required to be infected with a ChAd or HAdV-4 (which belongs to the same species E as the ChAds) at the same time. ChAds naturally circulate in chimpanzees which are not native in Australia. Thus, exposure of chimpanzee to the GMO is highly unlikely and the possibility of recombination occurring between GMO and ChAds is negligible.

155. As there is evidence of recombination occurring between human and non-human adenoviruses (Lasaro and Ertl, 2009; Roy et al., 2009; Wevers et al., 2011; Hoppe et al., 2015; Borkenhagen et al., 2019; Dehghan et al., 2019) and ChAds (e.g., ChAd68 and ChAd Y25) share about 90% sequence homology with the known sequence of HAdV-4 (Tatsis and Ertl, 2004).Therefore, there is a possibility for homologous recombination to occur if a person exposed to the GMO is also infected with HAdV-4 at the same time and in the same cells. This could result in the replication of GMO in the host causing over-production of spike proteins and subsequently adverse immune reaction.

156. HAdV-5 infections are common in humans and therefore, there is a possibility for a person exposed to the GMO to be co-infected with a HAdV-5. As mentioned in Chapter 1, Section 3.4, homologous recombination is restricted to members of the same species however homologous recombination with closely related adenoviruses species has been observed where high sequence homology occurs (Hoppe et al., 2015; Dehghan et al., 2019). The DNA homology between HAdV species is less than 20% (Ghebremedhin, 2014) and the GMO and HAdV-5 belongs to different species i.e., species E and C, respectively. Therefore, the homologous recombination between different species is less likely to occur due to differences in their sequence homology. The E1 flanking sequences of HAdV-5 and the SAdVs are different which further reduces the chance of site specific recombination (Tatsis and Ertl, 2004; Tatsis et al., 2006; Colloca et al., 2012; Ghebremedhin, 2014; Morris et al., 2016). In addition, the method used to insert the transgene into E1 gene of the GMO further decreases the likelihood of recombination with HAdV-5. This severely restricts homologous recombination and formation of replication defective HAdV-5 expressing spike protein or replication competent GMO without spike protein.

157. As recombination requires high sequence homology, there is limited possibility of recombination occurring between the GMO and the other viruses present in the exposed person.

158. The presence of pre-existing neutralising antibodies to HAdV (Lasaro and Ertl, 2009; Alonso-Padilla et al., 2016) in the exposed person would limit distribution and shedding of AdVs if homologous recombination occurs in the person exposed to the GMO.

159. Increased expression of spike protein in the host is unlikely to result in the production of novel toxic or allergenic compounds. The genome of the GMO including the introduced genes has been fully sequenced. These proteins are not known to be toxic to humans.

Potential harm

160. If complementation were to occur, the number of replication incompetent GMOs produced in the host cells would increase resulting in increased expression of spike proteins in the host. Similarly, homologous recombination would increase the expression of the introduced genes i.e., spike proteins. The exposed individuals may generate a stronger antibody response for the S glycoprotein of SARS-CoV-2 and also develop T-cell responses. These are not expected to cause harm to affected individuals. If the person exhibits any symptoms of adenoviral infection, effective antiviral treatments can be used to treat the infection.

161. As ChAds does not cause any disease in humans and other animals, the formation of a replication competent GMO without spike protein would not result in any harm. Similar to a previous study (Xiang et al., 2006), antibodies in humans could be formed in response to GM recombinant virus (GMO without spike protein) but no clinical symptoms would be expected.

Conclusion

162. The exposure of people to a GMO which has acquired the E1 gene or transferred spike proteins to other AdVs resulting in adverse immune response or disease in people or animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further assessment.

2.4.3 Risk scenario 3

Risk source	GMO
Potential causal pathway	Release of GMO into the environment via accidental spill/unused residues (e.g. sewerage, spills) ⬇ Exposure to people or animals ⬇ As per scenario 1-2
Potential harm	Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals

Risk Source

163. The source of potential harm for this postulated risk scenario is the GMO.

Potential causal Pathway

164. The GMO could be released in the environment through a spill during transport, storage or disposal where people or animals, including marine or aquatic animals could be exposed to the GMO. This could result in exposure of people and animals to the GMO and could potentially result in adverse immune reactions and/or disease in people and animals.

165. As discussed in Risk Scenario 1, the accidental spills associated with import, transport, storage and disposal have been considered and the proposed measures would reduce the chances of GMO being released into the environment.

166. In the event of a spill without correct decontamination with suitable disinfectants, the GMO could possibly persist/survive on surfaces for more than 12 weeks at low humidity (see Chapter 1, Section 3.5.4). In cold water or dark sediments, survival could be up to a few months (see Chapter 1, Section 3.5.4 and Section 4.3.3). This could result in the persistence of the GMO in the environment.

167. As mentioned in Chapter 1, Section 3 and 5.2, the ChAd is a member of the genus *Mastadenovirus* which infects a wide range of mammals including non-human primates, bats, felines, swine, canine, ovine and caprine (Roy et al., 2004; Borkenhagen et al., 2019). Therefore, it is possible that the GMO could infect other mammals including non-human primates. Given that the GMO is replication incompetent, this could result in infection but no replication and multiplication of the GMO in the other mammals.

168. As mentioned above, ChAd infection is limited to mammals only and is not known to infect insects, birds and non-mammalian marine organisms. Therefore, the likelihood of ChAd infecting other species in the Australian environment in highly unlikely.

169. Chimpanzees are the only natural hosts of ChAds and are not native to Australia and would only be found in zoos. The prevalence of wild-type ChAds in Australia would be very low and the impact of the GMO infecting the chimpanzee is also very low.

170. Similar to the parent organism, the GMO can persist in the environment however due to its non-replicating nature, the GMO would be unable to maintain a stable presence in the environment for long periods. Further, accidental spill/unused vials if not decontaminated appropriately could result in the presence of the GMO in the sewerage and subsequently GMO dispersal in the aquatic

environment. The impact of survival of the GMO in an aquatic environment is likely to be very low as the GMO is replication incompetent and would eventually degrade.

171. In the unlikely event that GMO is released into sewage water, it will be markedly diluted due to the small quantity of GMO present in a large volume of liquid waste or water. Therefore the likelihood of infection of humans or animals following exposure to an environmental source is remote.

172. Complementation and recombination could occur in the cells of co-infected animals in a similar way to the host as discussed in Risk Scenario 2.

Potential harm

173. Potential harms in this risk scenario would be the same as considered in the risk scenario 1 and 2 presented above.

Conclusion

174. The potential of GMO to be released into the environment and result in adverse immune reactions or disease in people or other animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further assessment.

Section 3 Uncertainty

175. Uncertainty is an intrinsic part of risk analysis[3]. There can be uncertainty in identifying the risk source, the causal linkage to harm, the type and degree of harm, the likelihood of harm or the level of risk. In relation to risk management, there can be uncertainty about the effectiveness, efficiency and practicality of controls.

176. There are several types of uncertainty in risk analysis (Clark and Brinkley, 2001; Hayes, 2004; Bammer and Smithson, 2008). These include:

- uncertainty about facts:
  - knowledge – data gaps, errors, small sample size, use of surrogate data
  - variability – inherent fluctuations or differences over time, space or group, associated with diversity and heterogeneity
- uncertainty about ideas:
  - description – expression of ideas with symbols, language or models can be subject to vagueness, ambiguity, context dependence, indeterminacy or under-specificity
  - perception – processing and interpreting risk is shaped by our mental processes and social/cultural circumstances, which vary between individuals and over time.

177. Uncertainty is addressed by approaches such as balance of evidence, conservative assumptions, and applying risk management measures that reduce the potential for risk scenarios involving uncertainty to lead to harm. If there is residual uncertainty that is important to estimating the level of risk, the Regulator will take this uncertainty into account in making decisions.

178. Overall, the level of uncertainty in this risk assessment is considered low and does not impact on the overall estimate of risk.

[3] A more detailed discussion is contained in the Regulator's *Risk Analysis Framework* available from the OGTR website or via Free call 1800 181 030.

179. Post release review (Chapter 3, Section 4) will be used to address uncertainty regarding future changes in knowledge about the GMO. This is typically used for commercial releases of GMOs, which generally do not have a fixed duration.

Section 4 Risk evaluation

180. Risk is evaluated against the objective of protecting the health and safety of people and the environment to determine the level of concern and, subsequently, the need for controls to mitigate or reduce risk. Risk evaluation may also aid consideration of whether the proposed dealings should be authorised, need further assessment, or require collection of additional information.

181. Factors used to determine which risks need treatment may include:

- risk criteria,
- level of risk,
- uncertainty associated with risk characterisation, and
- interactions between substantive risks.

182. Three hypothetical risk scenarios were identified whereby the proposed dealings might give rise to harm to people or the environment. This included consideration of whether people and animals can be exposed to the GMO while conducting the dealings and whether there is a potential for complementation and recombination of the GMO with other adenoviruses. The potential for the GMO to be released into the environment and its effects was also considered.

183. A risk is substantive only when the risk scenario may, because of gene technology, have some chance of causing harm. Risk scenarios that do not lead to harm, or could not reasonably occur, do not represent an identified risk and do not advance in the risk assessment process.

184. In the context of the control measures proposed by the applicant and the operating guidelines of the pertinent regulatory agencies, and considering both the short and long term, none of these scenarios was identified as representing a substantive risk requiring further assessment. The principal reasons for this include:

- The GMO is replication incompetent which will prevent it from multiplying in other cells;
- The GMO would be restricted to the site of injection and/or draining lymph nodes and would not be shed from the vaccine recipients;
- The GMO does not cause disease in humans and other organisms other than great apes;
- The consequences of accidental exposure to the GMO in people not being vaccinated (non-vaccines) would be minimised due to well-established import, transport, storage and disposal procedures; and

The likelihood of complementation and recombination of GMO with other adenoviruses is very low Therefore, any risks to the health and safety of people, or the environment, from the proposed commercial supply of the GM vaccine are considered to be negligible. The *Risk Analysis Framework* (OGTR 2013), which guides the risk assessment and risk management process, defines negligible risks as insubstantial with no present need to invoke actions for their mitigation. No controls are required to treat these negligible risks. Hence, the Regulator considers that the dealings involved in this proposed release do not pose a significant risk to either people or the environment[4]

[4] As none of the proposed dealings are considered to pose a significant risk to people or the environment, Section 52(2)(d)(ii) of the Act mandates a minimum period of 30 days for consultation on the RARMP.

Chapter 3 Risk management plan

Section 1 Background

185. Risk management is used to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan addresses risks evaluated as requiring treatment and considers limits and controls proposed by the applicant, as well as general risk management measures. The risk management plan informs the Regulator's decision-making process and is given effect through proposed licence conditions.

186. Under section 56 of the Act, the Regulator must not issue a licence unless satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in a way that protects the health and safety of people and the environment.

187. All licences are subject to three conditions prescribed in the Act. Section 63 of the Act requires that each licence holder inform relevant people of their obligations under the licence. The other statutory conditions allow the Regulator to maintain oversight of licensed dealings: Section 64 requires the licence holder to provide access to premises to OGTR inspectors and Section 65 requires the licence holder to report any information about risks or unintended effects of the dealing to the Regulator on becoming aware of them. Matters related to the ongoing suitability of the licence holder are also required to be reported to the Regulator.

188. The licence is also subject to any conditions imposed by the Regulator. Examples of the matters to which conditions may relate are listed in Section 62 of the Act. Licence conditions can be imposed to limit and control the scope of the dealings. In addition, the Regulator has extensive powers to monitor compliance with licence conditions under Section 152 of the Act.

Section 2 Risk treatment measures for substantive risks

189. The risk assessment of risk scenarios listed in Chapter 2 concluded that there are negligible risks to people and the environment from the proposed supply of the GMO. These risk scenarios were considered in the context of the proposed receiving environment and the Australia-wide release. The risk evaluation concluded that no containment measures are required to treat these negligible risks.

Section 3 General risk management

190. All DIR licences issued by the Regulator contain a number of conditions that relate to general risk management. These include conditions relating to:

- applicant suitability
- testing methodology
- identification of the persons or classes of persons covered by the licence
- reporting structures; and
- access for the purpose of monitoring for compliance.

3.1 Applicant suitability

191. In making a decision whether or not to issue a licence, the Regulator must have regard to the suitability of the applicant to hold a licence. Under Section 58 of the Act, matters that the Regulator must take into account include:

- any relevant convictions of the applicant
- any revocation or suspension of a relevant licence or permit held by the applicant under a law of the Commonwealth, a State or a foreign country

- the capacity of the applicant to meet the conditions of the licence.

192. If a licence were issued, the conditions would include a requirement for the licence holder to inform the Regulator of any circumstances that would affect their suitability.

193. In addition, any applicant organisation must have access to a properly constituted Institutional Biosafety Committee and be an accredited organisation under the Act.

3.2 Testing methodology

194. If a licence were issued, AstraZeneca would be required to provide a method to the Regulator for the reliable detection of the GMO, and the presence of the introduced genetic materials in a recipient organism. This methodology would be required prior to conducting any dealings with the GMO.

3.3 Identification of the persons or classes of persons covered by the licence

195. If a licence were issued, any person, including the licence holder, could conduct any permitted dealing with the GMO.

3.4 Reporting requirements

196. If issued, the licence would oblige the licence holder to immediately report any of the following to the Regulator:

- any additional information regarding risks to the health and safety of people or the environment associated with the dealings
- any contraventions of the licence by persons covered by the licence
- any unintended effects of the release.

197. The licence holder is also obliged to submit an Annual Report containing any information required by the licence.

198. There are also provisions that enable the Regulator to obtain information from the licence holder relating to the progress of the commercial release (see Section 4, below).

3.5 Monitoring for compliance

199. The Act stipulates, as a condition of every licence, that a person who is authorised by the licence to deal with a GMO, and who is required to comply with a condition of the licence, must allow the Regulator, inspectors or other person authorised by the Regulator, to enter premises where a dealing is being undertaken for the purpose of monitoring or auditing the dealing.

200. In cases of non-compliance with licence conditions, the Regulator may instigate an investigation to determine the nature and extent of non-compliance. The Act provides for criminal sanctions of large fines and/or imprisonment for failing to abide by the legislation, conditions of the licence or directions from the Regulator, especially where significant damage to the health and safety of people or the environment could result.

Section 4 Post release review

201. Regulation 10 requires the Regulator to consider the short and the long term when assessing risks. The Regulator takes account of the likelihood and impact of an adverse outcome over the foreseeable future, and does not disregard a risk on the basis that an adverse outcome might only occur in the longer term. However, as with any predictive process, accuracy is often greater in the shorter rather than longer term.

202. For the current application for a DIR licence, the Regulator is proposing to incorporate a requirement in the licence for ongoing oversight to provide feedback on the findings of the RARMP

and ensure the outcomes remain valid for future findings or changes in circumstances. If a licence was issued, this ongoing oversight would be achieved through PRR activities. The three components of PRR are:

- adverse effects reporting system (Section 4.1)
- requirement to monitor specific indicators of harm (Section 4.2)
- review of the RARMP (Section 4.3).

The outcomes of these PRR activities may result in no change to the licence or could result in the variation, cancellation or suspension of the licence.

4.1 Adverse effects reporting system

203. Any member of the public can report adverse experiences/effects resulting from a GMO to the OGTR through the Free-call number (1800 181 030), mail (MDP 54 – GPO Box 9848, Canberra ACT 2601) or via email to the OGTR inbox (ogtr@health.gov.au). Reports can be made at any time on any DIR licence. Credible information would form the basis of further investigation and may be used to inform a review of a RARMP (see Section 4.3 below) as well as the risk assessment of future applications involving similar GMOs.

4.2 Requirement to monitor specific indicators of harm

204. Collection of additional specific information on an intentional release provides a mechanism for 'closing the loop' in the risk analysis process and for verifying findings of the RARMP, by monitoring the specific indicators of harm that have been identified in the risk assessment.

205. The term 'specific indicators of harm' does not mean that it is expected that harm would necessarily occur if a licence was issued. Instead, it refers to measurement endpoints which are expected to change should the authorised dealings result in harm. Should a licence be issued, the licence holder would be required to monitor these specific indicators of harm as mandated by the licence.

206. The triggers for this component of PRR may include risk estimates greater than negligible or significant uncertainty in the risk assessment.

207. The characterisation of the risk scenarios discussed in Chapter 2 did not identify any risks greater than negligible. Therefore, they were not considered substantive risks that warranted further detailed assessment. Uncertainty is considered to be low. No specific indicators of harm have been identified in this RARMP for application DIR 180. However, specific indicators of harm may also be identified during later stages, e.g. following the consideration of comments received on the consultation version of the RARMP, or if a licence were issued, through either of the other components of PRR.

208. Conditions have been included in the licence to allow the Regulator to request further information from the licence holder about any matter to do with the progress of the release, including research to verify predictions of the risk assessment.

4.3 Review of the RARMP

209. The third component of PRR is the review of RARMPs after a commercial/general release licence is issued. Such a review would take into account any relevant new information, including any changes in the context of the release, to determine if the findings of the RARMP remained current. The timing of the review would be determined on a case-by-case basis and may be triggered by findings from either of the other components of PRR or be undertaken after the authorised dealings have been conducted for some time. If the review findings justified either an increase or decrease in the initial risk estimate(s), or identified new risks to people or to the environment that require management, this could lead to changes to the risk management plan and licence conditions.

Section 5 Conclusions of the consultation RARMP

210. The risk assessment concludes that the proposed commercial release of this GM COVID-19 vaccine poses negligible risks to the health and safety of people or the environment as a result of gene technology.

211. The risk management plan concludes that these negligible risks do not require specific risk treatment measures. However, if a licence were to be issued, general conditions are proposed to ensure that there is ongoing oversight of the release.

Chapter 4 Draft licence conditions

Section 1 Interpretations and Definitions

1. In this licence:

   (a) unless defined otherwise, words and phrases used have the same meaning as they do in the Act and the Gene Technology Regulations 2001 (the Regulations);

   (b) words denoting a gender include any other gender;

   (c) words in the singular include the plural and words in the plural include the singular;

   (d) words denoting persons include a partnership and a body whether corporate or otherwise;

   (e) references to any statute or other legislation (whether primary or subordinate) are a reference to a statute or other legislation of the Commonwealth of Australia as amended or replaced from time to time and equivalent provisions, if any, in corresponding State law, unless the contrary intention appears;

   (f) where any word or phrase is given a defined meaning, any other part of speech or other grammatical form in respect of that word has a corresponding meaning;

   (g) specific conditions prevail over standard conditions to the extent of any inconsistency.

2. In this licence:

'**Act**' means the *Gene Technology Act 2000* (Cth) or the corresponding State legislation under which this licence is issued.

'**Annual Report**' means a written report provided to the Regulator by the end of September each year containing all the information required by this licence to be provided in the Annual Report.

'ARTG' means the Australian Register of Therapeutic Goods maintained in accordance with the *Therapeutic Goods Act 1989*.

'**GM**' means genetically modified.

'**GMO**' means the genetically modified organism that is the subject of the dealings authorised by this licence.

'NLRD' is a Notifiable low risk dealing. Dealings conducted as an NLRD must be assessed by an institutional biosafety committee (IBC) before commencement and must comply with the requirements of the Gene Technology Regulations 2001.

'**OGTR**' means the Office of the Gene Technology Regulator.

'**Regulator**' means the Gene Technology Regulator.

Section 2 Licence conditions and obligations

3. This licence remains in force until it is suspended, cancelled or surrendered. No dealings with the GMO are authorised during any period of suspension.

4. The licence holder is AstraZeneca Pty Ltd.

5. Any person, including the licence holder, may conduct any authorised dealing(s) with the GMO.

6. The dealings authorised by this licence are:

   a) import of the GMOs;

   b) transport of the GMOs;

   c) disposal of the GMOs;

and the possession (including storage) and supply of the GMOs for the purposes of, or in the course, of any of these dealings.

Note: Use of the GMO for therapeutic purposes is not covered by the Gene Technology Act 2000 *and therefore this licence is not required to authorise such use. The GMOs are also subject to regulation by other federal and state departments and agencies, including the Therapeutic Goods Administration and the Department of Agriculture, Water and the Environment. These other departments and agencies may impose further requirements for, or limitations on, the use of the GMO or these dealings.*

7. This licence does not apply to dealings with the GMOs conducted as a Notifiable Low Risk Dealing (NLRD) or pursuant to another authorisation under the Act.

8. Dealings with the GMO may be conducted in all areas of Australia.

9. The licence authorises dealings with the GMO described in **Attachment A**.

Note: Attachment A is not included in the draft licence.

2.1 Obligations of the Licence Holder

10. The licence holder must immediately notify the Regulator if any of its contact details change.

Note: Please address correspondence to OGTR.M&C@health.gov.au

Prior to issuing a licence, the Regulator considers suitability of the applicant to hold a licence. The following conditions address ongoing suitability of the licence holder.

11. The licence holder must, at all times, remain an accredited organisation in accordance with the Act and must comply with its instrument of accreditation.

12. The licence holder must:

(a) inform the Regulator immediately in writing, of:

i. any relevant conviction of the licence holder; and

ii. any revocation or suspension of a licence or permit held by the licence holder under a law of the Australian Government, a State or a foreign country, being a law relating to the health and safety of people or the environment; and

iii. any event or circumstances that would affect the capacity of the holder of this licence to meet the conditions in it; and

(b) provide any information related to the licence holder's ongoing suitability to hold a licence, if requested, within the stipulated timeframe.

13. The licence holder must inform any person covered by this licence, to whom a particular condition of the licence applies, of the following:

(a) the particular condition (including any variations of it); and

(b) the cancellation or suspension of the licence; and

(c) the surrender of the licence.

2.2 Provision of new information to the Regulator

Licence conditions are based on the risk assessment and risk management plan developed in relation to the application using information available at the time of assessment. The following condition requires that any new information that may affect the risk assessment is communicated to the Regulator.

14. The licence holder must inform the Regulator if the licence holder becomes aware of:

(a) additional information as to any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or

(b) any contraventions of the licence by a person covered by the licence; or

(c) any unintended effects of the dealings authorised by the licence.

Note: The Act requires, for the purposes of the above condition, that:

(a) the licence holder will be taken to have become aware of additional information of a kind mentioned in paragraph 14 if he or she was reckless as to whether such information existed; and

(b) the licence holder will be taken to have become aware of contraventions, or unintended effects, of a kind mentioned in paragraph 14, if he or she was reckless as to whether such contraventions had occurred, or such unintended effects existed.

Note: Contraventions of the licence may occur through the action or inaction of a person.

15. If the licence holder is required to inform the Regulator under condition 14, the Regulator must be informed without delay.

Note: An example of informing without delay is contact made at the time of the incident via the OGTR free call phone number 1800 181 030, which provides emergency numbers for incidents that occur out of business hours.

16. If at any time the Regulator requests the licence holder to collect and provide information about any matter to do with the progress of the dealings authorised by this licence, including but not confined to:

(a) additional information as to any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence, whether or not the licence holder has provided information to the Regulator under condition 14(a);

(b) any contraventions of the licence by a person covered by the licence, whether or not the licence holder has provided information to the Regulator under condition 14(b);

(c) any unintended effects of the dealings authorised by the licence, whether or not the licence holder has provided information to the Regulator under condition 14(c);

(d) research, including by way of survey, to verify predictions of the risk assessment, or for any purpose related to risks to the health and safety of people, or to the environment;

(e) scientific literature and reports in respect of the GMO authorised by this licence, for a nominated period;

(f) details of any refusals of applications for licences or permits (however described) to deal with the GMO made pursuant to the regulatory laws of a foreign country;

and the request is reasonable, having regard to consistency with the Act and relevance to its purpose, then the licence holder must collect the information and provide it to the Regulator at a time and in the manner requested by the Regulator.

Note: The Regulator may invite the licence holder to make a submission on the reasonability of a request by the Regulator to collect and provide information relevant to the progress of the dealings with the GMO.

2.3 Obligations of persons covered by the licence

17. If a person is authorised by this licence to deal with the GMOs and a particular condition of this licence applies to the dealing by that person, the person must allow the Regulator, or a person

authorised by the Regulator, to enter premises where the dealing is being undertaken, for the purposes of auditing or monitoring the dealing.

Section 3 Reporting and Documentation Requirements

3.1 Notification of Authorisation by the Therapeutic Goods Administration

18. If the GMOs are included on the ARTG, the licence holder must notify the Regulator in writing within 14 days of registration.

19. The licence holder must notify the Regulator in writing of any subsequent amendments to the conditions of the ARTG registration involving the pattern of usage, handling, storage, transport or disposal of the GMOs, within 14 days of the change occurring.

3.2 Annual Report

20. The licence holder must provide an Annual Report to the Regulator by the end of September each year covering the previous financial year. An Annual Report must include:

(a) information about any adverse impacts, unintended effects, or new information relating to risks, to human health and safety or the environment caused by the GMOs or material from the GMOs;

(b) information about the numbers of GM vaccine doses imported and distributed to each State and Territory.

(c) information about the numbers of GM vaccine doses produced within Australia and distributed to each State and Territory.

3.3 Testing methodology

21. At least 14 days prior to conducting any dealings with the GMO, the licence holder must provide to the Regulator a written methodology to reliably detect the GMO, or the presence of the genetic modifications described in Attachment A in a recipient organism or environmental sample. The detection method(s) must be capable of identifying, to the satisfaction of the Regulator, each genetic modification event described in Attachment A.

Note: Please address correspondence to OGTR.M&C@health.gov.au

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Appendix A: Summary of submissions

The Regulator received several submissions from prescribed experts, agencies and authorities[5] on matters relevant to preparation of the RARMP. All issues raised in submissions relating to risks to the health and safety of people and the environment were considered. These issues, and where they are addressed in the consultation RARMP, are summarised below.

Submission	Summary of issues raised	Comment
1	Broadly supportive of application DIR 180.	Noted.
	While it is unlikely that there would be a risk to the food chain, this risk needs to be considered and the question addressed. Likewise, any risk to the environment and the ecosystem will also need to be addressed.	The risk to the environment and the ecosystem have been considered in Chapter 2 of the RARMP.
	Further reviews by the TGA and RARMP are required to ensure that the risk to public health and safety is minimal.	Noted.
	The vaccine has double-stranded DNA of the 'spike' protein, which is stable, rather than the single stranded RNA of the COVID-19 virus itself which is highly unstable. It is also stated that the clinical results were largely absent, but notes this will be the main focus of the TGA, which will be able to get more up-to-date results later after the UK data become available.	The safety, immunogenicity and efficacy of the GM vaccine from published clinical trials are discussed in Chapter 1, Section 4.3.
2	We have reviewed the material provided in the summary application. As the critical evaluations about the use or otherwise of this vaccine will be undertaken by the TGA, we are supportive of this application based on the current information provided while awaiting the RARMP at a later date.	Noted.
3	At this stage of the process, we highlight the importance of having strong systems in place for monitoring and follow-up any adverse impacts from the supply of the vaccine. I request that this be considered in the development of the consultation RARMP.	Draft licence conditions in Chapter 4 of the RARMP covers the monitoring and follow-up any adverse impacts from the supply of the vaccine. Impact in the vaccinated individuals will be assessed as part of the TGA assessment and requirements.

[5] Prescribed expects, agencies and authorities include GTTAC, State and Territory Governments, Australian government agencies and the Minister for the Environment.

Submission	Summary of issues raised	Comment
4	The supply appears to be of low risk to human health and the environment.	Noted.
	We had concerns about the potential for shedding of adenovirus vaccine vector from immunised humans into the sewage system, and the potential for the vector to recombine with human infective adenovirus, possibly resulting in an associated risk of harm to human health once in the receiving environment. We recommend that the Risk Assessment and Risk Management Plan very clearly address the perceived or actual risk of such recombination occurring. This will give the community confidence that there is no risk of adenovirus vaccine vector shedding into the environment.	The potential of the GMO to recombine with other adenoviruses has been considered in Risk scenario 2 (see Chapter 2, Section 2.4.2). The potential for the GMO to shed from the vaccinated person and into the environment is addressed in Chapter 1 Section 4.3.2 and Chapter 2, Section 2.4.3 (Risk scenario 3).
5	While it is likely that the environmental risks will be negligible for this vaccine, this is likely to be the first of several COVID-19 viral vaccine assessments and vaccination of the public is likely to be on a significant scale. Therefore, recommends full consideration and assessment of the following factors in the preparation of the RARMP. • Viral replication and shedding • Persistence • Host range • Recombination	The potential for viral replication, shedding, persistence, host range and recombination have been discussed throughout Chapter 1 (Section 3.4, 3.5.1, 3.5.2, 3.5.4, 4.3.2 and 4.3.3) and Chapter 2 (Risk scenario 2 and 3).
	Any recent information or data on risks such as zoonosis, recombination, host range changes associated with the use of GM adenoviruses should also be included in the RARMP.	Risks associated with GM adenoviruses has been included in Chapter 2.
6	Overall, supported the licence application of the AstraZeneca Pty Ltd and look forward to the release of the Risk Assessment and Risk Management Plan (RARMP) for the proposed commercial supply of COVID-19 vaccine.	Noted
	Essentially, no detail on the batch to batch consistency methods to be used, to test are provided in the document and believe that this section has not been completed adequately. Details on testing methods need to be provided, for both Australian and overseas manufacturing.	The GM vaccine may be manufactured overseas and/or in Australia. The Regulator has recently approved DNIR-630 and DNIR-632 for manufacturing and formulation of the GM vaccine. Batch to batch testing will be regulated by the TGA under cGMP licensing to the Australian and overseas manufacturing sites. The draft licence requires the applicant to provide a testing

Submission	Summary of issues raised	Comment
		method to reliably detect the GMO, and the presence of the introduced genetic materials in a recipient organism.
	What mechanisms will be implemented to ensure all administering sites comply with any TGA-mandated post release review requirements, including any adverse effect reporting as part of ongoing monitoring and oversight as well as ability to rapidly share information if required?	Noted. Adverse event reporting is included in the draft licence. This would also be considered by TGA under their assessment.
	Risk to the integrity of the vaccine if there are accidents during storage or transportation? E.g. power failure and temperature change. Will guidelines be developed to assist in decision-making in the event of uncertain integrity?	Noted. Effects of Improper storage and the impact on vaccine efficacy would be considered by TGA under their assessment. The Vaccine Storage Guidelines 'Strive for 5' provides information and advice for vaccine storage management for Australian immunisation service providers, from medical practices to large hospitals, clinics and outreach providers. These guidelines describe the best approach to ensure that clients receive effective and potent vaccines and provide advice on what should be done in the event of a cold chain breach.
	The survivability data presented in the application is inconsistent. This inconsistency must be clarified prior to use.	Chapter 1, Section 3.5.4 and Section 4.3.3 details the published data on survival of adenoviruses on various surfaces, water types and sediments.
	Risk to patients if vaccine administration is not intramuscular but is accidentally administered Intravenously or it is eaten? This may be highly unlikely but human error can occur.	The potential for contact with the GMO via other routes is discussed in the risk scenarios in Chapter 2. Risks to people receiving the vaccine would be considered by TGA under their assessment. The COVID-19 vaccination policy states that the States and Territories will be responsible for ensuring an appropriately qualified and trained workforce can support delivery of the vaccine. More details about the COVID-19 vaccination policy can be found at

Submission	Summary of issues raised	Comment
		https://www.health.gov.au/resources/publications/australian-covid-19-vaccination-policy
	Raised concerns about aerosolization/ vaporisation of the vaccine if spilled/vial broken or other risks to the healthcare professional delivering the vaccine, which might be increased by use of a multi-dose vial?	The potential for aerosol formation, spilled/broken vial and risk to the healthcare professionals have been addressed as part of Risk scenario 1 (Chapter 2, Section 2.4.1).
	Are there any additional concerns regarding adenovirus-naïve patients (children) or immunocompromised persons?	Risks associated with direct use of the vaccine would be considered by the TGA in their assessment.
	Is there a risk to animals/wildlife if wastewater or general waste/clinical waste in the disposal of unused product?	The potential risk to animals/ wildlife is discussed in Risk scenario 3 (Chapter 2, Section 2.4.3).
	Risk at manufacturing locations to workers, environment and wildlife. Consider by-products in process.	The potential risk of exposure of people during preparation and administration and handling of the GM vaccine is discussed in Risk scenario 1 (Chapter 2, Section 2.4.1). The risk to manufacturing individuals for Australian manufactured GM vaccine is considered as part of DNIR-630 and DNIR-632 assessment.
	Are there any short or long-term effects on the utility of tetracyclines in the vaccinated population if leakage in wastewater/flora/fauna etc?	The vaccine does not contain tetracycline. It contains a CMV promoter with a tetracycline operator site. This tetracycline operator site does not confer resistance to tetracyclines.
	Consider how outback/nursing posts/no air-conditioning situations will be managed to meet the expected conditions for site of Australian release.	See above re COVID-19 vaccination policy.
	This application doesn't seem to have a sustainability/climate change lens. Are there any opportunities to have a lower waste footprint that	Issues relating to sustainability are outside the scope of the Regulator's assessment required by the Act.

Submission	Summary of issues raised	Comment
	could be explored? Should this be done at a state/territory level?	These issues are the responsibility of the States and Territories.
7	**Draft recommendations**	
	The committee agrees that the following should be included in the RARMP: potential accidental exposure of humans and other organism to the GMO resulting in harm, potential for complementation and recombination of the GMO and other adenoviruses and potential for GMO to be harmful to the environment.	Noted.
	The committee also suggested to consider risks associated with: • possible integration of the adenoviral DNA into human genomes; and	The potential for random integration of vector DNA is discussed in Chapter 1 (Section 3.4 and 4.3.1) and Chapter 2 (Section 2.2.).
	• appropriate methods for decontaminating any spills.	Appropriate decontamination methods are discussed in Chapter 1, Section 3.5.4.